Musculo-Skeletal Stress Markers in Bioarchaeology: Indicators of Activity Levels or Human Variation? A re-analysis and Interpretation.

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Declaration

None of the material in this thesis has been previously submitted for a degree in this or any other university. This thesis is the result of my own work.

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Table list (with abbreviated description)

Figure lists (with abbreviated description)

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Abstract

Musculoskeletal stress markers (MSM) have been widely used by bioarchaeologists as indicators of physical activity (Jurmain 1999). These stress markers occur at the sites of the attachment of soft tissues (muscle, tendon, ligament, fascia and menisci) to bone. They are anomalies of bone formation or destruction at these sites and often called enthesopathies in clinical literature. The aims of this research were firstly, to determine the aetiology of these features; in particular, whether they can be used as indicators of physical activity. Secondly, to create a new digital and quantifiable recording method, that is both cheap and simple to use.

To achieve the first aim, several literature reviews were undertaken. The first was a review of the bioarchaeological literature. This covered the majority of methods used to study activity levels in human skeletal remains. This was undertaken to determine which questions bioarchaeologists were asking of their samples and which methods were the most commonly applied. MSM were included to establish which recording methods were most commonly used and how the data were interpreted. The second literature review covered the anatomy of the attachment sites (also called entheses). This research demonstrated that the bioarchaeological recording methods did not take into account differences in normal anatomy. These differences were found to be so great that they would seriously compromise any data collected using the bioarchaeological methods. The third literature review covered the relationship between trauma and enthesopathy formation. This demonstrated that the link between activity-related stress and enthesopathy formation was complex and not a simple, direct relationship. The final literature review covered the relationship between enthesopathy formation and disease. Many diseases, for example DISH and ankylosing spondylitis, were found to be associated with enthesopathy formation. The findings of these literature reviews indicated that current bioarchaeological recording methods and interpretive practises are at odds with the clinical literature.

The second aim had to take these factors into account. Pilot studies were undertaken to develop a new recording method. The final method used visual recording and

measurement of entheses along with digitisation of the surface in two-dimensions using a profile gauge. The digital curves were then quantified using roughness parameters commonly used in materials science. These described the surfaces and could also be used to determine whether this method was applicable to differentiate between normal entheses and those with enthesopathies. Discriminant function analysis demonstrated that this was possible. Stringent diagnostic criteria were also set in place to remove any individuals with possible disease-related enthesopathies. Using the same method, it was found that these could (in some circumstances) also be differentiated from the normal samples. In summary, it was found that a new bioarchaeological recording method was required for MSM and that the new method was simple to use and that the quantification allowed for differentiation between normal entheses and those with enthesopathies.

Keywords

Musculoskeletal stress markers (MSM), entheses, enthesopathy, boneforming, Fishergate House, York.

Chapter 1: Introduction and Aims

1.1 Importance of occupational stress markers in archaeology and related disciplines

Clinically, occupational medicine is an important and burgeoning field. It encompasses the disciplines of psychology, but more importantly for this study, pathology and trauma related to occupation. The first comprehensive medical text to discuss the association of occupation and disease is Bernardino Ramazzini's *De Morbis Artificium Diatriba* originally published in 1700 (Ramazzini 1983). The text describes diseases and disorders common in various occupations, from gilding to soap-making, all based upon his studies of workplaces and existing knowledge (Franco 1999). Today, the World Health Organisation estimates that 217 million cases of occupational illness and 250 million cases of work-related injuries occur worldwide every year (Rosenstock, *et al.* 2006). Occupational disease and injury is therefore of extreme significance to human life both in the past and at present.

In the bioarchaeological literature pathological changes thought to be caused by occupational disease and injury have been widely used to reconstruct activities and task division in archaeological skeletal populations. It has been used to reconstruct tool use (Peterson 1998), study temporal trends in activity (Al-Oumaoui, *et al.* 2004) and sexual division of labour (Bourbou 2003). Recently, the applicability of some methods has been questioned. The use of degenerative joint disease (DJD), for example, was studied by Jurmain (1999), who found contradictory evidence for and against its suitability as an indicator of activity. The other primary method for studying activity in archaeological human skeletal remains is the presence of musculoskeletal stress markers (MSM, or clinically called enthesopathies; Jurmain 1999). This means the study of sites of attachment for tendon, ligament and muscle to the skeleton. There is now a considerable body of bioarchaeological literature using this method (discussed in Chapter 2). Some authors have even stated that different types of MSM have different aetiologies (Hawkey and Merbs 1995). MSM are ideal

for the study of activity because they relate directly to muscle or joint use. Therefore, it may be possible to determine not only which joints were heavily used, but the direction of loading on them.

1.2 Aims

The primary aim of this research is to determine whether MSM can be used as indicators of physical activity. For this to be the case there would have to be a direct link between repetitive stress and MSM presence. The secondary aim of this research is to develop a new recording method for MSM, which is based on the normal anatomy and other aetiological factors. This method should be simple, repeatable, cheap and ideally quantitative. It should be cheap and simple so that it is readily usable by other researchers and for this reason it should also be repeatable (low intra- and inter-observer error rates). It should be quantitative to allow for statistical analysis of the data.

To achieve these aims a review of bioarchaeological literature, anatomical literature, and clinical literature on the aetiology of enthesopathies will be necessary. The bioarchaeological review will provide information on current methods used by bioarchaeologists for studying activity-related stress in archaeologically derived skeletal remains and the most common methods of recording MSM. Anatomical literature will provide a basis for understanding whether these recording methods reflect the anatomy of these sites under normal and abnormal conditions. The aetiology of enthesopathies will then be discussed in relation to physical stress and disease. This will be performed to determine which enthesopathies represent repetitive physical activity (if any) and to develop methods to avoid recording enthesopathies caused by diseases as MSM.

These reviews will form the background for creating a new recording method. This will be tested on skeletons from late medieval Fishergate House, York, England to determine its repeatability, user-friendliness and most importantly its efficacy.

1.3 Definitions

To avoid confusion the following definitions are used throughout, unless otherwise stated:

- **Enthesis** (plural: entheses): this is the attachment site (either the origin or the insertion) of muscle, tendon, ligament and joint capsule to bone (Benjamin, *et al.* 2002).
- **Enthesopathy** (plural: enthesopathies): any deviation from the normal appearance/biochemistry of an enthesis. This terminology implies abnormality at the site of the enthesis. Common causes of enthesopathies are trauma and disease, for this reason it is thought this term is justified for the description of these sites. Changes occurring with the aging process are also included under the term enthesopathy. This term is also the most common clinical term for the description of these changes and, because of the clinical background of this research, it seems sensible to be consistent with this literature in the use of this term. In the majority of the clinical literature, this term does not connote suffering.
- **Musculoskeletal stress marker** (MSM): This is the terminology commonly used in the bioarchaeological literature for enthesopathies when discussed in the context of activity-related stress. This term will only be used when discussing bioarchaeological literature.
- **Bone formers**: individuals with a propensity to have enthesopathies. By definition in this thesis, this requires enthesopathies at the sacroiliac joint and in the spine. This term will be defined further in Chapter 6. Note that this is not the definition proposed by Rogers and colleagues (1997), because the presence of osteophytes is not required.
- **Activity-related stress** (or occupational stress): any change in physical state caused by activity or occupation.

1.4 Structure

The first aim of this thesis is addressed via literature reviews. The first literature review assesses the bioarchaeological approaches to understanding and recording activity-related stress. Different recording methods are discussed, alongside MSM. Following this, the second literature review focuses on the fundamentals of MSM: the anatomy of the entheses. Without understanding this, it is difficult to comprehend how a recording method can be developed for MSM. The primary feature of MSM is that, by definition, they are indicators of activity-related stress. Consequently, the relationship between trauma, activity-related stress (such as sports and occupational injuries) and MSM was elaborated in the third literature review. It was clear from the anatomical literature that one of the most common causes of enthesopathy formation was disease, such cases cannot be referred to as MSM because they are basically unrelated to activity-related stress.

The second aim of this thesis was to create a new recording method. This had to take into account the findings of the literature reviews. Materials and pilot methods were discussed in the following chapter, along with the method which was used in the main study. The results of this study and their utility were presented and the penultimate chapter discusses the findings in relation to hypotheses set out in the Materials and Methods chapter. The final chapter summarises the findings, along with the limitations of this study and requirements for future analysis.

Chapter 2. Background to Markers of Occupational Stress

2.1 Introduction

This chapter presents a critical review of bioarchaeological literature on "occupational" stress. MSM are the primary focus of this thesis, but this section will also discuss the myriad other methods employed. The other methods include robusticity, biomechanical analysis, and degenerative joint disease (DJD). The aims of this chapter are to collate the research methods previously used, and to categorize the research questions they have been used to answer. References to conference abstracts have been included in this section to provide further evidence of the types of research questions that scientists would like to apply these techniques to. However, it is understood that these are not fully peer-reviewed and that because of their length cannot provide details about methods or results. Nevertheless, they do provide information about the types of research questions asked and therefore do provide useful information for this chapter. Further goals are to identify gaps in our knowledge of this field and to consider the appropriateness of the techniques used. The ultimate aim of this chapter is to determine how the role of enthesopathies as MSM can be better understood in relation to activity.

The first medical text to discuss the association of occupation and disease is Bernardino Ramazzini's *De Morbis Artificum Diatriba* written in 1700 (Ramazzini 1983). The text describes diseases and disorders common in various occupations, from gilding to soap-making, all based upon his studies of workplaces and existing knowledge (*ibid.*). Today, the World Health Organisation estimates that 217 million cases of occupational illness and 250 million cases of work-related injuries occur worldwide every year (Rosenstock, *et al.* 2006). Occupational disease and injury is therefore of extreme significance to human life both in the past and at present. In this chapter and the rest of this thesis, activity-related stress, or occupational stress, is defined as any change in physical state caused by activity or occupation. This will primarily mean change to the skeleton caused by mechanical stress, *e.g.* movement. However, occupational diseases leaving traces on the skeleton will also be discussed.

The phrase "markers of occupational stress" or MOS has been used in the bioarchaeological literature to cover any change on the human skeleton thought to be caused by activity-related or occupational stress. This term will be used in this definition in the present chapter. Modern clinical medicine includes psychological stress under the umbrella of occupational stress (McDonald 2000), but this is not included in this definition, because psychological stress is unlikely to directly change bone.

2.2 Uses and Abuses of MOS

Evidence, in the form of human skeletal remains, is not the only data on occupation and activity-levels in the past. Historical, ethnographic and archaeological sources provide considerable data on the lives of individuals in the past. However, none of these methods rely on data collected directly from the individuals who lived in the past. Theoretically, human skeletal remains should, therefore, be ideal for studying the lives of people in the past. However, it is evident that where possible all sources of data should be considered, because understanding activity-patterns in isolation from other data, limits its potential use.

Common research questions involve testing theories about activity-level differences within populations, for example sex and status differences (Al-Oumaoui, *et al.* 2004; Larsen 1997). Temporal and spatial differences, for example comparisons of activity-levels between hunter-gatherers and agriculturalists, are studied by comparing populations (Larsen 2000). Studies comparing hypothetical populations, if performed correctly, provide comparative as opposed to absolute data. This means that it may be possible to state that one group was more active than another, but not how much more active. However, comparing data sets can only be performed if the data are comparable, *i.e.* the same type of data has to have been collected, age ranges must be comparable and inter- and intra-observer error must be minimal. This can be difficult for subjective data sets, as will be discussed below. Hence, one of the aims of this research is to create an objective recording scheme for MSM.

The role of bioarchaeological data has to be clearly indicated, as there have been examples of misuse. It has been noted (Jurmain 1999) that cases have occurred in which bioarchaeological evidence has been used to strengthen archaeological arguments, while simultaneously the archaeological evidence has been used to confirm the interpretation of the bioarchaeological data. Such circular arguments must be avoided at all costs, as they undermine the potential strength of combining data sources. This concern is important not only in the present chapter and thesis, but for this research field as a whole.

2.3 Methods of Occupational Stress Analysis in Bioarchaeology

Occupational stress in this context is physical stress caused by occupation or frequent activity (such as hunting, for example), causing bone deformation (*e.g.* increase in cortical thickness or bone spur formation). Psychological stress related to occupations, although an important field in clinical studies, will not be considered, as discussed above. The remaining chapter will be divided into geometric properties (*e.g.* cross-sectional geometry) and MOS, which includes DJD and MSM. Both of these are based on the principle that deformation of bone from occupational stress is possible because of continuous re-modelling of bone throughout life. Longitudinal growth of long bones ceases in adolescents when the growth plates between the epiphyses and metaphyses ossify. However, cells in the bone remain active leading to both the deposition and removal of bone on active surfaces, *e.g.* the trabeculae, and periosteal and endosteal surfaces. Regions marginal to joints and entheses can also form bone leading to osteophytes and enthesopathies, respectively (Jurmain 1999). It is known that mechanical stimulus can activate this process, but how this stimulus is transmitted to cells is not fully understood.

In general, it is thought that bone optimises itself for its mechanical role as the support for the soft tissues (Currey 2002). Consequently, all the active surfaces listed above have been the object of interest for bioarchaeological studies of occupational stress. The thickness and shape of bone shafts have been studied for robusticity and cross-sectional area (Ruff 1992). The pattern of trabeculae has been studied to indicate direction of loading forces and thereby function, primarily in comparisons between

non-human primates or hominins and modern humans .(Maga, *et al.* 2006; Ryan and van Rietbergen 2005). The prevalence and distribution of both osteophytes (Jurmain 1991) and enthesopathies (Hawkey and Merbs 1995) have also been studied. The focus of this research has been on the latter because of their close relationship with specific muscle activity and, therefore, limb movements.

2.3.1 Robusticity and Biomechanical Analysis

Robusticity and biomechanical analysis have been grouped together because they are both measures of the size and shape of bone. Robusticity is defined here as the external measurements of bones and the calculation of their indices. In contrast, biomechanical analytical methods, such as cross-sectional geometry, take into account the dimensions of the medullary cavity. Some studies have combined robusticity and biomechanical analysis (Bridges 1989; Marchi, *et al.* 2006; Sparacello and Marchi 2008; Stock and Shaw 2007). Such research demonstrates that, although cross-sectional geometry takes into account dimensions of the medullary cavity, both robusticity and biomechanical analysis techniques are using the geometric characteristics of the bone to provide functional information. In fact, it has been stated that:

'Indices derived from external diameters are only estimates of cross-sectional properties that are more exactly measured through sophisticated methods such as computed tomography' (Cole 1994) p. 221)

but these indices "are highly correlated with more precisely measured results and should, therefore, yield comparable interpretations" (ibid.)

However, it is not clear from the literature how highly correlated these are (Cole 1994; Knüsel 2000; Larsen 1997). It has also been found that external measurements do not relate to changes occurring internally and can indicate patterns contrary to those found using cross-sectional geometry (Bridges, *et al.* 2000). The determination of robusticity and the interpretation of measurements will be returned to in Chapters 6

and 7, where they are used to characterise the size and shape of bone in relation to MSM formation.

2.3.1.1 Robusticity

Robusticity is a measurement of the size and shape of a bone. In this section only the dimensions from measurements of whole bones will be discussed. Bone sections (whether sectioned by saw or computed tomography [CT]), will be discussed in relation to cross-sectional geometry. The most commonly used bone for studying upper limb use is the humerus; whilst the femur is most often used for the lower limb. *In vivo b*one is deposited and removed on both endosteal and periosteal surfaces of these bones, but methods of robusticity assessment can only take into account the latter. This is a considerable limitation of the method. However, it is a useful starting point, as most of the data can be gained using the measurements described in standard osteological texts (Bass 1995; Brickley and McKinley 2004; Buikstra and Ubelaker 1994) and are, therefore, recorded by most bioarchaeologists. Other measurements deemed useful are taken from pre-determined landmarks which are decided upon on the basis of the research question.

In some cases robusticity indices are calculated (Imber pers. comm.; (Carlson, *et al.* 2007; Cole 1994; Formicola, *et al.* 1990; Mays, *et al.* 1999)), in others the raw measurements are compared using statistical tests (Benfer and McKern 1966; France 1988; Porter 1999a; Steele and Mays 1995). The differences in approach to these data depend on the research questions. A further limitation of this method is that deformation of the bone caused by pathological changes or trauma must be recognised and such bones excluded from these studies to avoid biasing the results. The effect of enthesopathy formation at or near to the landmarks measured is also a problem. Changes at these sites may not represent the same type of loading as that affecting the dimensions of the bone as a whole (*e.g.* enthesis hypertrophy may occur because of one-off traumatic events) and may compromise data collected.

Sexual dimorphism, *i.e.* the skeletal differences between males and females, provides key data on the different roles of males and females within a population and is a theme commonly explored both within and outside the field of activity-related changes. This will be returned to frequently in this chapter in the context of activity-related differences. Sexual dimorphism in this context is used to measure differences in size and shape of male and female bones to determine differences in activity patterns, in part because of dietary change (long bone length is often used as a proxy for stature, which is affected by diet; Roberts and Manchester 2005), but also because of loading differences (studied using robusticity and long bone shape; Marchi *et al.* 2006). It has been hypothesised that sexual dimorphism is greater in hunter-gatherer populations than agriculturalists. This is because males have a longer growth period and so can catch-up on growth during calorific abundant periods (Cole 1994). Bayendor and Martin (1989) found that, although stature was sexually dimorphic (indicating a hunter-gatherer lifestyle), robusticity was similar in both males and females, indicating that both sexes led lives with similar activity-levels. In contrast, Cole (1994) studied the sexual dimorphism in size of Plains Indians across this supposed subsistence strategy shift from a hunter-gatherer to agricultural economy. No change in sexual dimorphism in length was found indicating that their sedentary life raising corn, along with hunting for meat, provided few periods of dietary stress (*ibid.*). However, sexual dimorphism in shape did occur in both the hunter-gatherer and agriculturalist samples, the latter indicating differences in daily activity. Cole (*ibid.*) hypothesised that this reflects the primary role of women in the later sample as agriculturalists, with men as meat providers, *i.e.* in part living a hunter-gatherer lifestyle.

Population based skeletal analysis, as opposed to case studies, are thought to provide the ability to compare such activities at different sites and make inferences about the significance of findings Questions relating to subsistence patterns seem to be the most common, but often status and sexual differences are also studied (Arriaza and Standen 2006; Bridges, *et al.* 2000; Cole 1994; Knüsel 2000; Velemínský, *et al.* 2005). Cole (1994), as discussed above, compared hunter-gatherer and agricultural limb robusticity. Arriaza and Standen (2006), in comparison, compared the robusticity of humeri to test the hypothesis that agricultural societies have greater task division: *e.g.* individuals were either fishermen or farmers, but not both. Growing and processing

crops, along with tool use changes and sexual differences in labour patterns have also been explored (Bridges, *et al.* 2000). Status divisions were tested in Moravia by comparing robusticity and burial location (Velemínský, *et al.* 2005).

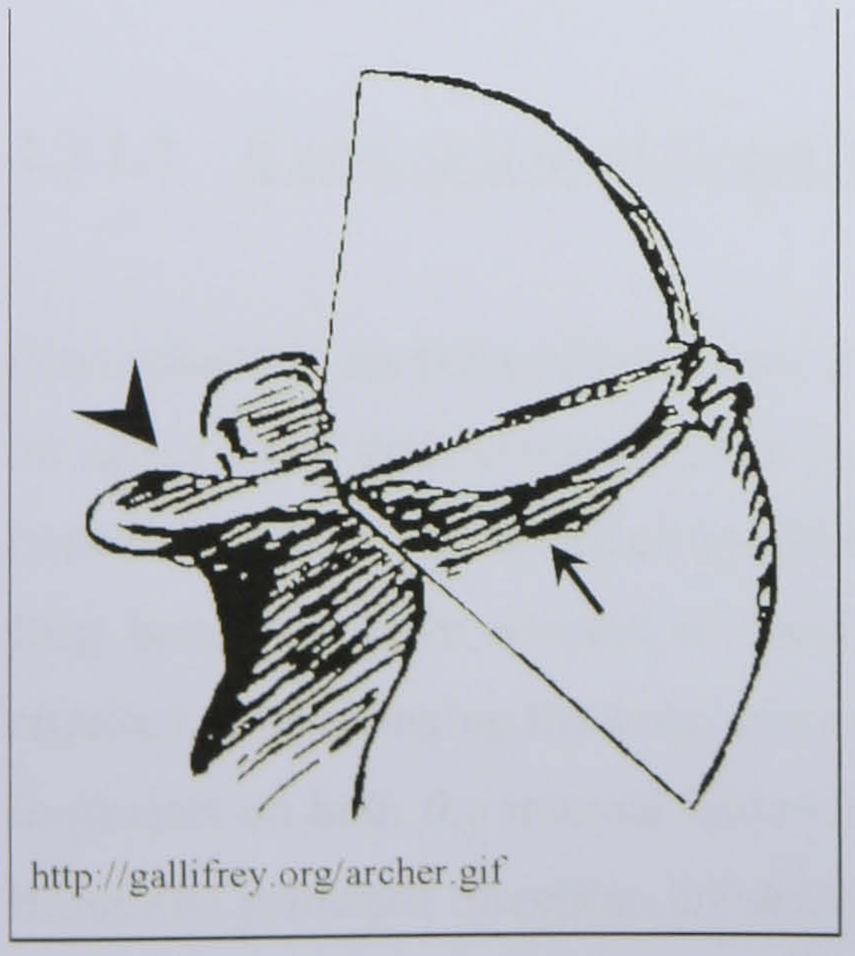
A mass grave from the time of the Wars of the Roses (1455-1487) has been found associated with the Battle of Towton (29th of March 1461), North Yorkshire, England. Although documentary sources exist for some individuals involved in the battle, the majority were anonymous (Fiorato, *et al.* 2001). Although this predates the existence of standing armies, it was not known whether the individuals could be considered professional soldiers (Knüsel 2000). Robusticity was used to compare the humeri from Towton with those of males from the late medieval Gilbertine priory at Fishergate, York. The lack of statistically significant differences between the length, humerus robusticity (the robusticity index as defined by Bass 1995, p. 152) and a clavicular-humeral robusticity index was thought to indicate that the dead at Towton were not professional soldiers, nor were they chosen for the battle based on stature or physique (Knüsel 2000).

Handedness is not necessarily directly related to activity patterns, but precision tasks are normally carried out with the dominant hand, and it has also been discovered that the dominant arm utilises more efficient muscle torques, than the opposite side (Sainburg 2002). It is possible that this is the cause of the size asymmetry between the dominant and non-dominant hand. The basis of handedness is not fully understood. However, there is a general right-sided predominance and an increased trend towards right-handedness with increasing age (Porac and Coren 1981). A large (780 individuals) study of adult human humeri from pre-industrial and industrial individuals spanning the globe demonstrated that right hand bias has existed since early modern humans and Neanderthals evolved (Auerbach and Ruff 2006). They also found that asymmetry in industrial samples is not as great as in pre-industrial samples, perhaps indicating a reduction in mechanical loading with time and mechanisation. However, diaphyseal breadth was found to be more variable than either long bone length or articular surface size, and this may indicate that these latter are under greater genetic control. The presence of asymmetry in both clavicles, which supported MSM data of asymmetrical arm use (Mays, *et al.* 1999), humerus and radius has also been noted in a sample from medieval Wharram Percy, but it is unclear which specific

activities caused this (Mays, *et al.* 1999; Steele and Mays 1995). However, the ulna, even in modern athletes, has been found to be less dimorphic and the clavicle shorter on the dominant side (Steele 2000).

Several problems have been described with this method of studying activity (in relation to preferential hand and upper limb use). It has been found that the position of measurements on the humerus affects the data in such a way that skeletons appear right-side dominant in their proximal humerus, but left-side dominant in the distal humerus (Knüsel 2000). This was discovered in the skeletons from the mass grave at Towton. Knüsel interprets this as an indication of these individuals being involved in archery in which both upper limbs are mechanically loaded, but at the opposite ends of the same bones (Figure 2.1). However, no reports of this occurring in modern archers have been found in the clinical data (from a search of Medline July 2006). The second problem is that of paralysis of a limb. A case from Italy has been described (Churchill and Formicola 1997) with marked asymmetric robusticity of the humerus. There is no obvious pathology, but nerve damage or muscle atrophy (which has multiple causes) may not be visible on skeletal remains. Ruling out such cases may prove difficult when assessing robusticity but, if included, may skew results.

Figure 2.1 Archer, demonstrating loading of proximal (arrow head) and distal humerus (arrow) in right and left arms respectively.



http://gallifrey.org/archer.gif

Physique is also a factor that is difficult to account for in skeletal remains. Attempts have been made to estimate *in vivo* body weight from skeletal remains (Daneshvari and Pearson 2004; Porter 1999a; Ruff, *et al.* 1991), but some methods have been found to correlate with weight during growth (*e.g.* femoral head size as discussed by Ruff *et al.* 1991). Physique and weight are particularly important in the lower limb, because greater body weight increases the forces affecting the locomotor system. This is demonstrated by the propensity for obese individuals to require treatment for degenerative joint disease of the hip and knee (Brandi, *et al.* 2001). A weak correlation exists between skeletal measurements and types of physique (estimated on live individuals; Porter 1999). Currently, there is no method to account for the effect of weight or physique on bone dimensions, MSM formation or degenerative joint disease. It is possible that this compromises data because skeletons of obese individuals will wrongly indicate that these people have been highly active because of these degenerative changes.

Measurements do have some advantages, though. There are cheap and non-destructive. Osteological measurements are clearly described in the basic bioarchaeological textbooks (Bass 1995; Brothwell 1981) and both the British (Brickley and McKinley 2004) and North American (Buikstra and Ubelaker 1994) recording standards advise their use. Consequently, comparisons of large data sets can be made to answer questions about robusticity and growth. For this reason common long bone measurements will be used in this research (see Chapters 6 and 7).

2.3.1.2 Cross-sectional Geometry

Biomechanical analysis of bone geometry involves the modelling of loading patterns on bones from their cross-sectional geometric properties. Because of the ability of bone to re-model [as described by Wolff's law (Currey 2002)] it is assumed that the long bone will have adapted to "best suit" its purpose by depositing bone where required, thus changing the bone's cross-sectional geometry (as described above bone re-models on both the internal and external surfaces). By treating the long bone as a beam, the principal directions of stress can be measured (Ruff, *et al.* 2006). This is achieved by studying sections of bone and calculating the amount of bone along the x-

and y-axes which run perpendicular to the long axis (called the neutral or central axis and often defined as a centre line) of the bone. At this neutral axis the stress distribution is zero, but increases with distance to the maximum point found in the outermost fibres. The area of the bone (often designated CA meaning cortical area) and the second moment of area can be calculated. From the former it is possible to study compressive and tensile stress and from the latter it is possible to calculate the bending stresses (I_a) and torsional stresses (J_a). The orientation of maximum bending strength, θ, can also be calculated. Raw data can be used for calculating relative differences (*e.g.* I_x/I_y), but size standardisation based on long bone length (squared or cubed) is considered necessary when comparing sexes or populations (Ruff 1994). In general the rounder a section of the femur is (*i.e.* the closer I_x/I_y is to 1) the more sedentary the individual was (Larsen 2000).

Jurmain (1999), in his review of this field, concluded that biomechanical analysis avoids the confusion and difficulties of using MOS, because of the soundness of the underlying hypothesis and the quantitative, rather than qualitative, nature of the results gathered. Clinical evidence on the relationship between cross-sectional geometry and activity patterns is minimal. The one exception is clinical evidence of geometric changes resulting from playing tennis. However, this is evidence taken from elite tennis players and, as Jurmain (1999) points out, drawing conclusions from such restricted samples is problematic. However, further research into activity-patterns and bone geometry could help to resolve this caveat. Recent advances, such as computerised image processing and non-destructive sectioning methods have made this approach faster and bone geometry can, therefore, be used on larger population samples (Ruff 1992; Sailer, *et al.* 2003). Ruff (1992) also points out the importance of relating biomechanical findings to more traditional methods of research, such as metrical analysis, DJD patterns and bone histomorphometry.

The most commonly used methods of creating these bone sections are either direct sectioning of bone or computed tomography. In addition, X-radiography has been used. In X-radiography cortical thickness is calculated from the bone width minus medullary cavity width [bones are positioned antero-posteriorly and medio-laterally]. The cortical index is then calculated from the cortical thickness divided by bone width

and multiplied by 100. Bending stress (I_a) can be estimated based on either a circular or an elliptical cross-section (Mays 1999, 2001: O'Neill and Ruff 2003; Stirland 1998: Weiss 2005). This is a cheaper and less destructive method than either sectioning or computed tomography but even if these measures are standardised by body mass and long bone length, they are not as accurate as cross-sectional properties (Stock and Shaw 2007).

A more critical problem is recognition of the other factors affecting bone geometry apart from activity (Bice 2003; Jurmain 1999; Ruff, *et al.* 2006; Ruff, *et al.* 1991) . These include weight (Ruff, *et al.* 1991), hormones (Bice 2003; Devlin 2004), genes, diet and age (Bice 2003). The location of the cross-section must also be chosen with reference to anatomy because of possible effects of local soft tissue attachments, which change the thickness and shape of the bone (Morgan, *et al.* 2006). Such factors must be taken into account during both data collection and interpretation. If this is done, then biomechanical analysis might be one of the best approaches to measuring activity-levels in archaeological samples. It should also be recognised that the data obtained can only be used to study trends or patterns, not as absolute values, because of the many assumptions that have to be made if biomechanical modelling of the bone is based on its beam-like properties (Lieberman, *et al.* 2004; Rybicki, *et al.* 1972).

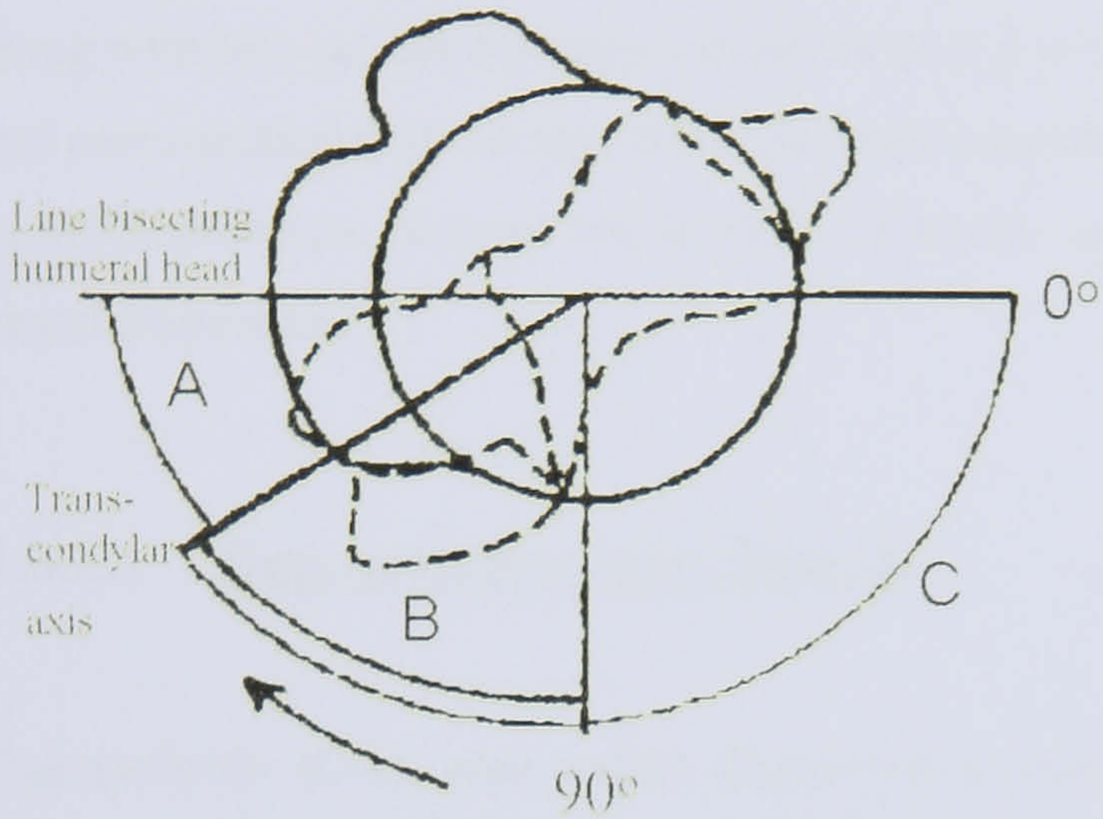
The primary use of cross-sectional geometry has been to compare activity patterns in different populations (primarily hunter-gatherers versus agriculturalists) (Aldridge, *et al.* 1998; Bridges 1989; Bridges, *et al.* 2000; Brock 1985; Brock and Ruff 1987; Carlson, *et al.* 2007; Larsen 2000; Ledger, *et al.* 2000; Marchi 2006; Marchi, *et al.* 2006; Ruff 1994; Ruff, *et al.* 2005; Zabecki, *et al.* 2004). Others have compared blade injured and non-injured individuals (Knüsel 2000; Rhodes and Knüsel 2006), prisoners of war with normal populations (Weiss 2005) and manual versus non-manual labourers (Mays 2001; Mondragón and Pearson 2003). Cross-sectional geometry has also been applied to individuals with pathological changes (Churchill and Formicola 1997) and those with trauma-related disuse atrophy (Nystrom and Buikstra 2004). Differences between the sexes have also been studied (Beauchesne, *et al.* 2004; Bridges, *et al.* 2000; Lazenby 1998; Marchi, *et al.* 2006).

What is clear is that there are no modern clinical models for any of these activities (Jurmain 1999). Nor are the activities of groups such as hunter-gatherers homogenous (Carlson, *et al.* 2007). The differences in diet, gene pool, and age distribution on bone mechanics and cross-sectional geometry probably all have confounding effects (Bice 2003). Again, these factors have not been fully studied in clinical cases because of the difficulty in studying actual loading patterns *in vivo* and, apart from the study of osteoporosis, such research is rarely useful for either the treatment or the understanding of diseases. Animal models do exist, but are affected by the same problems and may not be good proxies for human research. The applicability of treating a long bone as a beam has also been questioned (Mucci 1987) because of a lack of congruity between hypotheses and experimental results.

2.3.1.3 Humeral Retroversion

Humeral retroversion is the angle between the transcondylar axist of the distal humerus and an imaginary line bisecting the humeral head (see Figure 2.2). This has only rarely been used to study activity. This may, in part, be because of the lack of clinical literature to support its use (Rhodes 2006). Differences in retroversion between the left and right sides are used to study activity patterns. One North American study found that retroversion was associated with robustness and bone density, but that less than 50% (4./11) of the sample studied demonstrated retroversion asymmetry (Gjerdrum, *et al.* 2003). A similar (called humeral torsion) study (Rhodes 2006) was applied to medieval skeletons (some associated with battles and some not) from across England along with a modern North American sample. This study found no statistically significant bilateral asymmetry, but there were statistical differences within some groups (blade injured versus non-injured and male versus female). However, Rhodes (*ibid.*) thought that there was not enough clinical literature to fully ascertain the relationship between activity and "humeral torsion". Rhodes also stated that the individual differences were being masked by population heterogeneity.

Figure 2.2 Humeral retroversion. Adapted from (Rhodes 2006). Angles A, B, and C are all used.



2.3.1.4 Robusticity and Biomechanical Analysis: Conclusions

Further research is required in both external measurements and cross-sectional geometry to understand the relationship between activity or loading patterns on bones and how to control for factors, such as diet and age (Bice 2003). Although these are serious problems, both of these methods have the advantage of being reproducible and of being quantitative rather than qualitative assessments of skeletal remains. This is important, particularly for human remains which are to be reburied, because the data can be re-used readily even if its interpretation changes. Qualitative recording methods often go hand in hand with the interpretations of the results. Additionally, as will be seen in the next section, the recording of both DJD and enthesopathies relies on, mostly, non-standardised recording techniques and subjectivity.

2.3.2 Markers of Occupational Stress (MOS)

Markers of occupational stress (MOS) are well-delimited changes to the skeleton, such as new bone formation. This section includes discussion of both DJD and MSM, along with less commonly used indicators such as non-metric traits. Unlike robusticity and cross-sectional geometry, these are rarely recorded as quantitative data. Typically, in MOS, presence, absence and severity of lesions are recorded based on macroscopic visual inspection.

2.3.2.1 Degenerative Joint Disease

Osteoarthritis (OA), also called degenerative joint disease (DJD) to highlight its perceived mechanical aetiology, is a disease of the synovial joints. Clinically, a combination of genetic and environmental factors are thought to contribute to the onset of this disease (Brandi, *et al.* 2001; Greenfield and Goldberg 1997; MacGregor and Keen 1999). Primary OA involves the breakdown of normally smooth hyaline cartilage leading to its fibrillation, but the exact mechanism of this process is poorly understood (Dandy and Edwards 1999). Further joint movement creates friction leading to further break down. Unlike bone, hyaline cartilage does not re-model, but the subchondral bone can and this is normally seen as osteophyte formation. This can lock the joint, but in cases where the joint is still mobile, but where hyaline cartilage is absent, the bone surfaces rub together causing eburnation. The rate of these changes is dependent on multiple intrinsic and extrinsic factors, such as joint use and the biochemistry of the local cartilage (Kuettner and Cole 2005). Secondary DJD can also occur in association with mal-aligned fractures (Jurmain 1999; Neri and Lancellotti 2002), congenital deformities (Jurmain 1999), spondylolithesis (Merbs 2001) and any other condition that changes joint biomechanics or proprioception (Jurmain 1999). However, this review focuses on the use of DJD patterns to indicate occupation and activity-related stress (Jurmain 1999; Knusel 2000). The success of this approach and recording methods used will be discussed below.

The hypothesis that mechanical loading contributes to DJD is put succinctly by Ruff (1992, p. 53). He stated that because articular surface area cannot change in adults in response to loading, the only part of the bone able to remodel is the underlying trabeculae. These become more dense leading to stiffening (*i.e.* its inability to deform in response to stress) of joint surfaces. This leads to an increase in stress in the joint cartilage because the bone itself is no longer able to cushion the joint upon impact. This leads to cartilage degeneration and reaction of both subchondral bone and bone around the margins of the joints, leading to osteophyte formation (Rogers and Waldron 1995). The most commonly affected joints are the knee and hip in modern populations and this is generally considered to be related to weight-bearing. However, it has been discovered that cartilage has varying properties in different joints and that this is why the ankle, a very important weight-bearing joint, is rarely affected (Kuettner and Cole 2005). It is also important to stress that in clinical literature males and females have different susceptibilities to DJD: both differences in joint patterns and frequency are noted (Brandi *et al.* 2001). This is important to recognise because research has been published on sexual differences in activities based on DJD patterns (Jurmain 1999). It is possible that these differences reflect normal sexual dimorphism.

The relationship between mechanical loading and DJD is not clear cut. There have been many epidemiological studies with contradictory conclusions on the effect of repetitive stress on DJD presence (Chitnavis, *et al.* 2000; Jurmain 1999). In the archaeological literature rates of DJD have been compared between manual and non-manual workers buried at Christ Church, Spitalfields, London (a post-medieval crypt population) and no statistical differences were found in the appendicular skeleton (Waldron 1993). However, DJD of the spine was more common in non-manual workers. This might, in part, be because weak muscles and non-usage of limbs are, perhaps counter-intuitively, also predisposing factors to DJD (Shakoor and Moisio 2004). Comparisons between modern and archaeologically derived populations have also been made (Crubezy, *et al.* 2002; Rogers and Waldron 1995). These studies have found that prevalence and distribution patterns of DJD differ between these populations. This may be caused by the recording methods used (Crubezy *et al.* 2002), but may relate to genetic, environmental or occupational differences (Crubezy *et al.* 2002; Rogers and Waldron 1995). This may also be caused by differences in age distribution of the samples.

Despite the contradictory clinical evidence for occupational-related DJD, many palaeopathological papers have been published based on this association, and the questions asked are identical to those asked by researchers using other techniques, *i.e.* evidence for changes, or differences, in either subsistence strategy or common activities (*e.g.* grinding corn, domestic chores); sexual differences in labour have also been researched. Primarily, this is achieved by studying differences in disease patterning (*i.e.* joints or side of the body affected), but also by quantifying DJD presence in a sample (Bourbou 2003; Bridges 1992; Ciranni and Fornaciari 2003; Cope, *et al.* 2005; Davidson, *et al.* 2002; Denton 2002; Derevenski 2000; Jurmain 1991; Jurmain and Kilgore 1995; Larsen, *et al.* 2002; Larsen and Williams 2003; Morfin, *et al.* 2002; Pinsolle and Vandermeersch 2002; Saunders, *et al.* 2002; Sciulli and Oberly 2002; Ubelaker and Newson 2002; Wedel and Rankin-Hill 2004; Wilczak and Kennedy 1998). Ciranni and Fornaciari (2003) found that in the skeleton of the cellist (and composer) Luigi Boccherini the distribution of DJD (and MSM) in his skeleton, could be directly linked to joint usage during cello playing. DJD was found in Boccherini's thumbs, interphalangeal joints, and in the articular facets of the spine (probably related to posture). Temporal trends are commonly found and are thought to indicate changes in activity, but it may be possible that other factors are partly responsible. Population differences have also been found, but whether this relates to the age distribution of the sample, to activity differences or other causes of DJD cannot (in most cases) be determined.

One of the other main considerations in recent reviews is the scoring of DJD in skeletal remains. It has been recommended (Jurmain 1999; Rogers and Waldron 1995) that only "severe" cases of DJD, *i.e.* only cases with eburnation (which proves that cartilage has been removed) should be recorded as DJD, to avoid recording age-related osteophyte formation. Clinical grading systems for use on cadavers use the presence of fibrillation of the cartilage and presence or erosion of cartilage as the primary diagnostic tools (Table 2.1). Note that these criteria make no mention of either porosity, subchondral bone eburnation or wear grooves, which have also been described (Rogers and Dieppe 1993), which are all key features of palaeopathological

diagnostic criteria. The relationship between porosity and DJD is, therefore, poorly understood.

Table 2.1 Clinical diagnostic criteria for osteoarthritis in cadavers (Kuettner and Cole 2005).

Grade	Description	Palaeopathological use
0	No changes, smooth cartilage	Changes not visible on bare bone
1	Fibrillation, pits and/or grooves. No change to joint surface shape	
2	Fibrillation, fissuring, pitting. Marginal hyperplasia and small osteophytes	Marginal osteophytes may be visible (dependent on good preservation). Stages 2 and 3 are indistinguishable on bare bone
3	Extensive fissuring and change to joint surface shape. 30% or less of cartilage eroded.	
4	30% or more of cartilage eroded. Osteophytes prominent, joint surface shape changed.	Marginal osteophytes visible.

It is noted in two earlier works, (Jurmain 1991; Jurmain and Kilgore 1995), that scoring joints separately at different regions on a scale of severity enables both statistical analysis of the data and a better understanding of the changes occurring both within and around each individual joint. However, it has also been found that inter-observer error for the recording of DJD is very high, except in cases where eburnation is present (Waldron and Rogers 1991). The American *Standards for Data Collection from Human Skeletal Remains* (Buikstra and Ubelaker 1994, p.122-123) use the following criteria for diagnosis of DJD:

'LIPPING, DEGREE

8.1.1 Barely discernible

8.1.2 Sharp ridge, sometime curled with spicules

8.1.3 Extensive spicule formation

8.1.4 Ankylosis

LIPPING, EXTENT OF CIRCMFERENCE AFFECTED BY MOST SEVERE EXPRESSION

8.2.1 <1/3

8.2.2 1/3-2/3

8.2.3 >2/3

SURFACE POROSITY, DEGREE

8.3.1 Pinpoint

8.3.2 Coalesced

8.3.3 Both pinpoint and coalesced present

POROSITY, EXTENT OF SURFACE AFFECTED

8.4.1 <1/3

8.4.2 1/3-2/3

8.4.3 >2/3

EBURNATION, DEGREE

8.5.1 Barely discernible

8.5.2 Polish only

8.5.3 Polish with groove(s)

EBURNATION, EXTENT OF SURFACE AFFECTED

8.6.1 <1/3

8.6.2 1/3-2/3

8.6.3 >2/3'

However, even these standards allow the observer considerable interpretive power and are unlikely to reduce inter-observer error rates.

As with the data on MSM (discussed in the following section) many of the papers do not state clearly the recording methods used (Douglas, *et al.* 1997; Lai and Lovell 1992; Malim and Hines 1998; Steen and Lane 1998; Stirland 2000; Williams 1994). Most of these papers do not add anything to the discussion of DJD in the context of this review. However, one paper is notable for its discussion of MSM presence in relation to DJD (Steen and Lane 1998). This preliminary analysis demonstrated that DJD patterns echoed the MSM data in the Alaskan population studied. Whether similar findings occurred in other populations is unknown, but this would tally with the hypothesis that individuals with enthesopathies and those that develop DJD have a genetic propensity to form bone (Jurmain 1999; Rogers, *et al.* 1997). In particular, both are associated with sex and increased age (Cardoso 2008; Weiss and Jurmain 2007).

Advantages and disadvantages of these respective systems are similar to those discussed in the following section on MSM. The system used depends on hypotheses regarding DJD development *i.e.* whether severity is recorded or not. Problems with statistical analysis of MSM data also apply here, as do the problems of intra- and inter- observer error. These problems will not be discussed here for two reasons, firstly they will be discussed in detail in the next section and secondly the applicability of using DJD to measure activity-levels is questionable at best, because of its multifactorial aetiology.

To conclude, DJD patterns as a record of activity-related stress have been virtually discredited by Jurmain (1999) and should according to the British guidelines for recording human remains (Roberts and Connell 2004) never be used alone as an indicator of activity. However, DJD was used by The Global History of Health Project as an indicator of workload and activity (Steckel, *et al.* 2006). There may still be a role for DJD as an indicator of activity when combined with other forms of bioarchaeological evidence (but the age-at-death of the sample must be controlled for). Clear population differences in DJD prevalence and patterns have been discovered and these require further analysis, as is occurring in large population studies (Roberts and Cox 2003; Steckel, *et al.* 2006; Steckel and Rose 2002), and in relation to clinical data to further our understanding of DJD itself.

2.3.2.2 Musculoskeletal Stress Markers

Musculoskeletal stress markers (MSM) are abnormalities at the sites of tendon, ligament, muscle, or joint capsule attachment to bone (called entheses). The abnormalities are often called enthesopathies (and do not refer only to bone spurs, but also to lytic lesions) in clinical literature, reflecting their multifactorial aetiology. The study of MSM is founded in the effect of physical stress (*e.g.* manual labour) on enthesopathy formation. The next few chapters will be used to determine whether there is a direct link between enthesopathies and physical stress and how they should be interpreted by bioarchaeologists. This chapter focuses on the current use (and as will be discussed, misuse) of enthesopathies as MSM in palaeopathology.

MSM can be seen on skeletons as spurs (Figure 2.3), lytic lesions (Figure 2.4), a combination of the two (Figure 2.4) or rough patches (Figure 2.6). Woven bone has also been seen as these sites, by this author (Figure 2.7). The lesions form at the sites of movement-related soft tissue attachments, *i.e.* tendon, ligament, muscle and joint capsule. It is because of this relationship with movement that palaeopathologists have used MSM as indicators of the repetitive movement that occurs in daily occupation or other frequent activities. MSM are also considered more useful than DJD because they represent specific muscle use and can, theoretically, be used to assess the type of movement (*e.g.* flexion or extension) of a limb. These are the reasons for their popularity.

Figure 2.3 White arrow showing a bone spur at the lateral epicondyle of the humerus at the common extensor origin. A spur at the medial epicondyle (common flexor origin) is also visible.

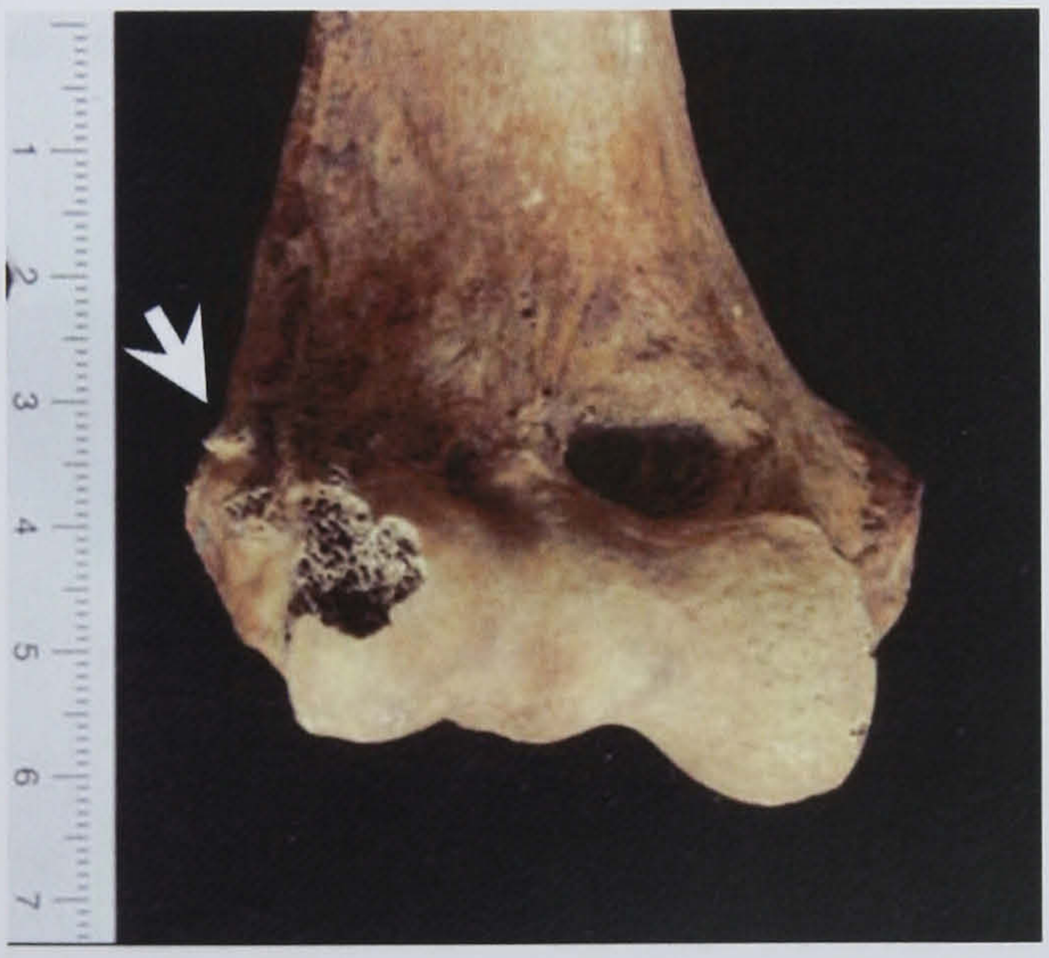


Figure 2.4 Lytic lesions at *biceps brachii* insertion.

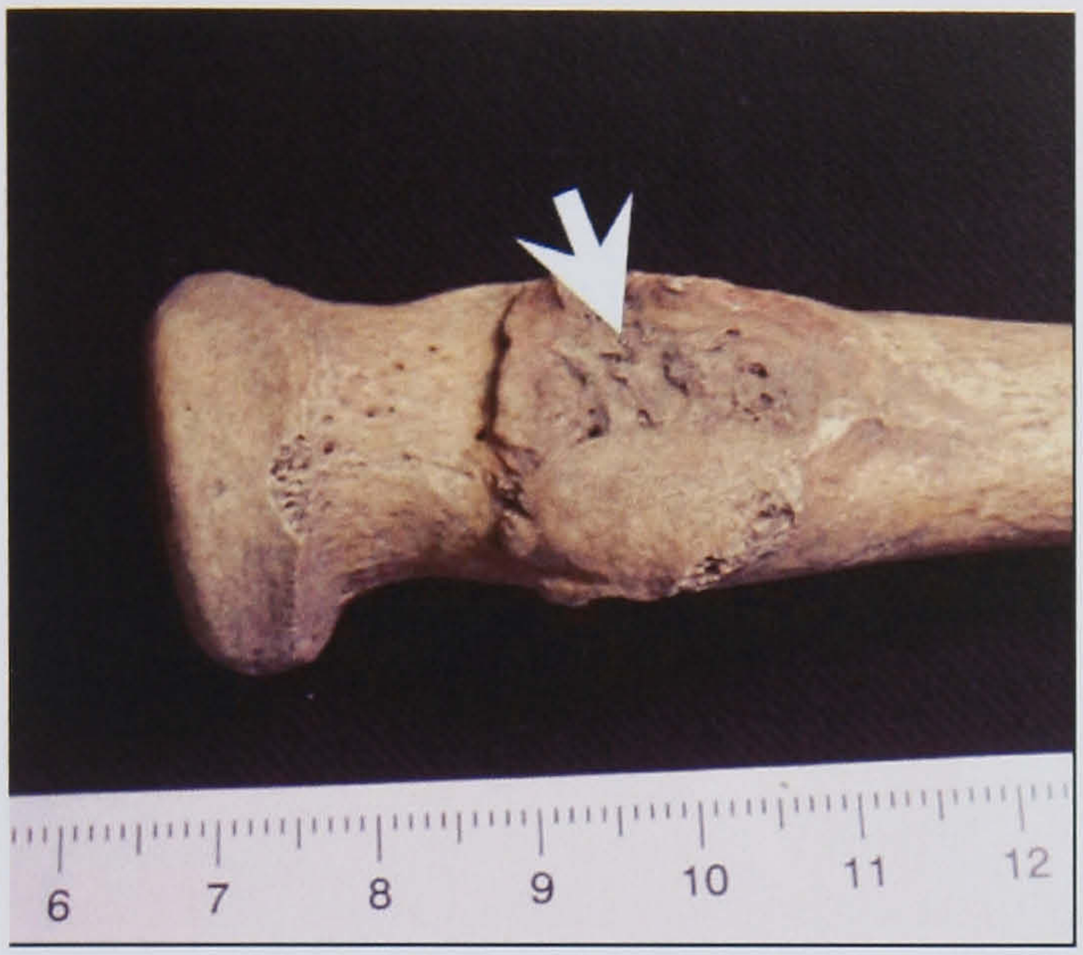


Figure 2.5 Bone formation and lytic lesion at the enthesis of the costoclavicular ligament on the medial end of the inferior side of the clavicle. White arrow showing new bone formation, grey arrow showing lytic lesion.

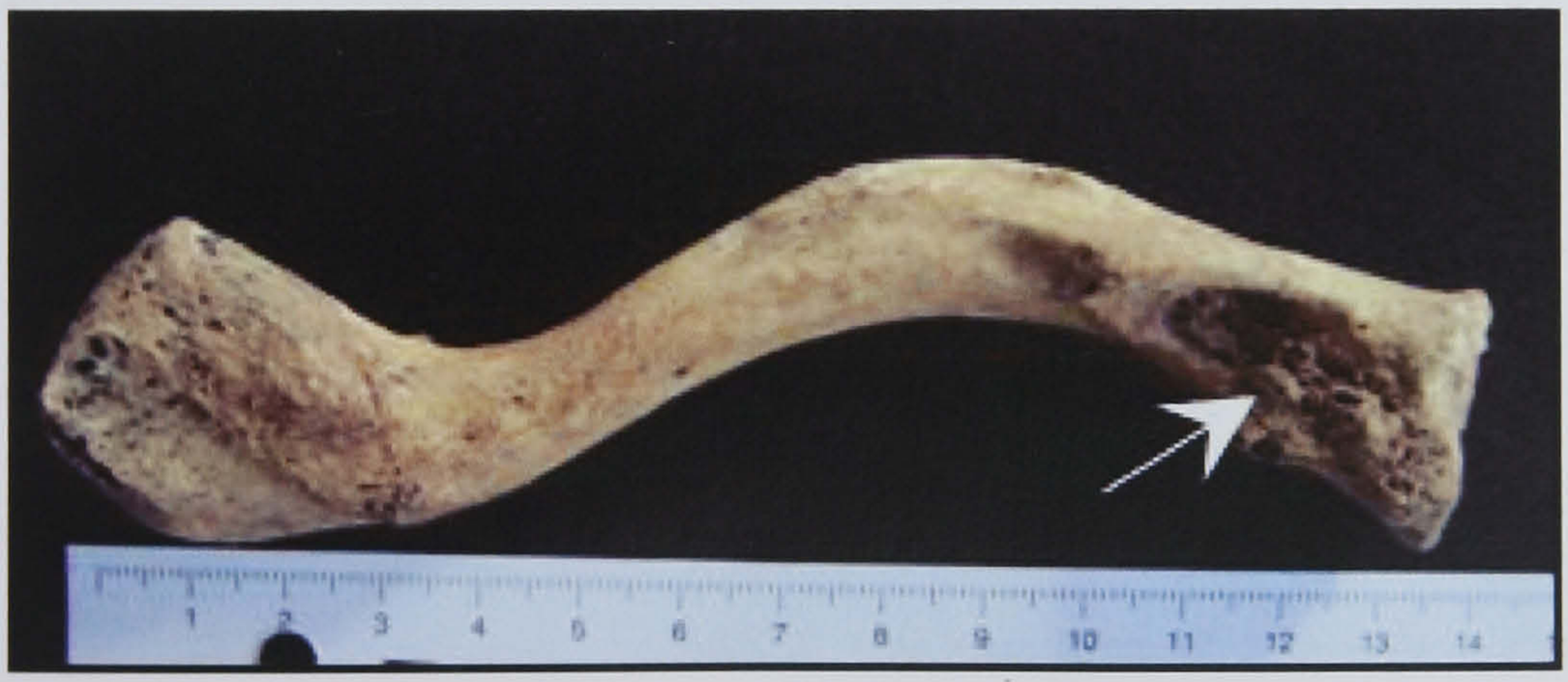


Figure 2.6 Roughness at the soleal line (white arrow) at the proximal end of the posterior side of the tibia.

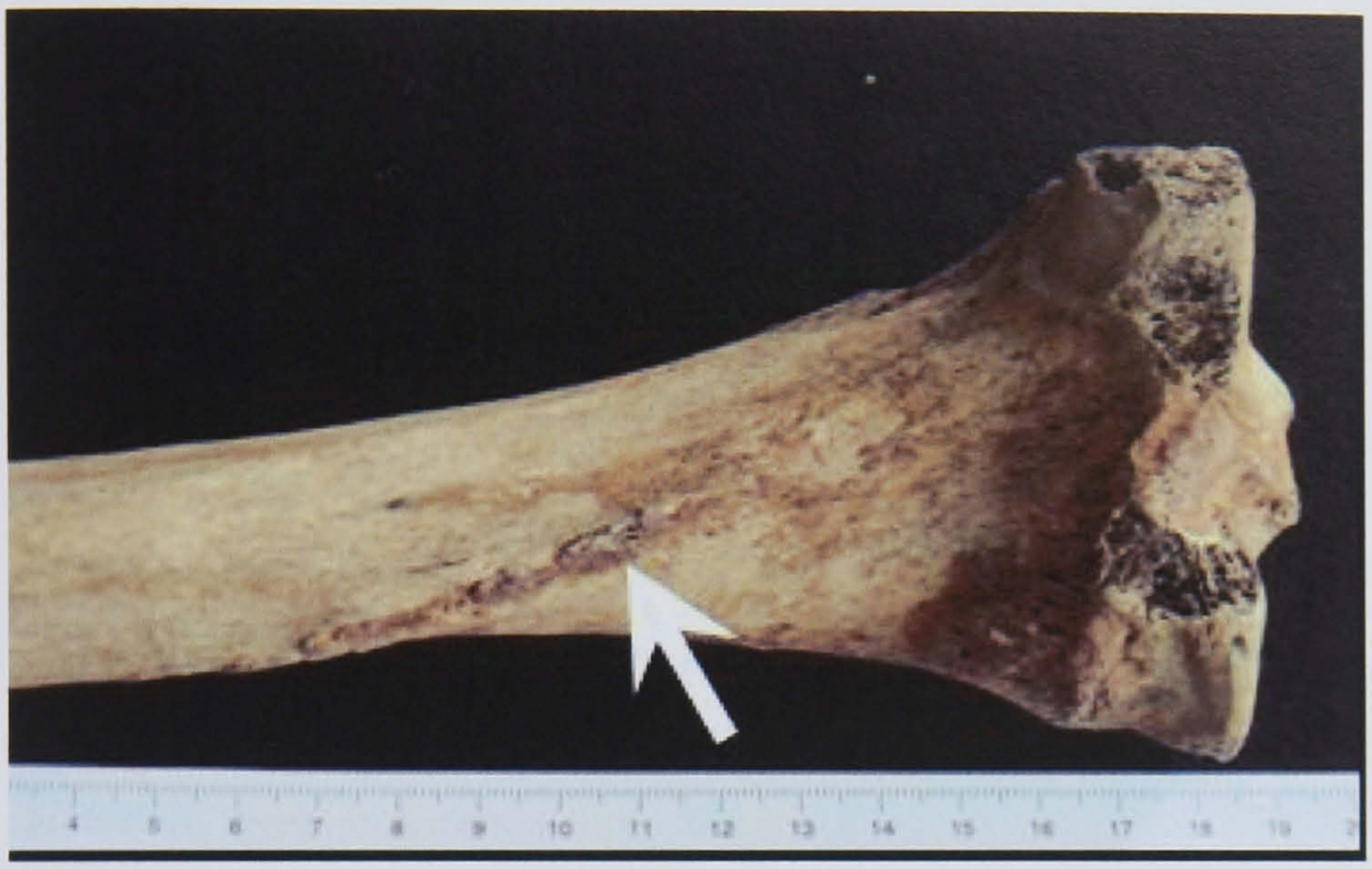


Figure 2.7 Woven bone on the surface of the *biceps brachii* insertion on the left proximal radius. Skeleton F 204 Fishergate House, York.

Like all markers of occupational stress, MSM have been put to extensive use. Their primary use has been to compare different populations or samples; for example male or female, hunter-gatherers versus agriculturalists, high status or low status (Al-Oumaoui, *et al.* 2004; Benus and Masnicova 2002; Berget and Churchill 1994; Bridges 1997; Chapman 1997; Cope, *et al.* 2004; Denton 2002; Drapeau 2006; Dutour

1986; Hartnett 2002; Hawkey 1988; Hawkey and Merbs 1995; Hawkey and Street 1992; Knusel 1993; Molleson 1994; Molnar 2006, 2008; Neri and Lancellotti 2004; Rodrigues-Carvalho, *et al.* 2002; Silva, *et al.* 2002; Steen and Lane 1998; Terranova, *et al.* 2000; Toyne 2003; Velemínský, *et al.* 2005; Wedel and Rankin-Hill 2004; Wells, *et al.* 2003; Zabecki 2006). However, some researchers have used MSM to study individuals (Ciranni and Fornaciari 2003; Hawkey 1998; Knusel and Goggel 1993; Lazenby and Pfeiffer 1993; Molleson and Hodgson 2003; Neri and Lancellotti 2004; Oates, *et al.* 2008; Wells, *et al.* 2003) and others to answer questions about tool use (Kennedy 1983; Neri and Lancellotti 2004; Peterson 1998) or other specific aspects of life, for example handedness (Churchill and Morris 1998; Clark 1999; Denton 2002; Hayden, *et al.* 2004; Knüsel 2000; Lai and Lovell 1992; Lovell and Dublenko 1999; Mays, *et al.* 1999; Rabey 2006; Stirland 2000). Some researchers have studied known occupation samples (Mariotti, *et al.* 2004, 2007; Villotte 2006). However, these researchers have found that age is one of the most important factors in enthesopathy formation.

These papers have demonstrated population differences where expected from archaeological, historical and in some cases ethnographic data. They, therefore, seem to corroborate the hypothesis that MSM are activity-related. Sexual differences in MSM patterns have also widely been found and are thought to indicate sex-specific activities. However, MSM sexual dimorphism may occur in populations without activity differences (perhaps in relation to biological factors, such as hormone levels), this cannot be known until studied in greater detail. These broad trends using fairly large sample sizes may hide the other causes of enthesopathy formation such as diseases (Chapter 5). This is also a problem for smaller-scale studies, in which individual variation have a greater effect on data collected. Many studies do not discuss the process of eliminating disease-related enthesopathy formation. In the case of Hawkey (1998), enthesopathy formation was used to investigate the range of movements that a young female with a bone-forming disease was capable of. However, there is no clinical data indicating that using enthesopathies to indicate ranges of movement in such diseases is possible.

Several reviews exist concerning MSM (Jurmain 1999; Kennedy 1989, 1998; Knusel 2000; Wilczak and Kennedy 1998); many of the occupational stress markers listed in

(Capasso, *et al.* 1999) are enthesopathy related, and an entire volume of the International Journal of Osteoarchaeology (1998 volume 8 issue 5) has been devoted to this subject. These reviews stress the importance of considering:

- the age distribution of a sample (enthesopathies, like DJD, are more common in older individuals) (Jurmain 1999; Knüsel 2000);
- the inability of MSM to indicate a specific occupation or activity and the importance of studying distribution rather than individual enthesopathy presence (Kennedy 1998);
- the importance of standardised recording criteria (Kennedy 1998; Wilczak and Kennedy 1998) with the latter authors stressing the need for quantitative and not qualitative methods;
- the lack of experimental verification for MSM as indicators of activity (Jurmain 1999; Wilczak and Kennedy 1998);
- the need for clinical (particularly sports medicine) literature reviews to resolve aetiological questions (Jurmain 1999; Kennedy 1989).

In general, there is a lack of evidence presented in this literature supporting the hypothesis of a direct relationship between musculoskeletal stress and enthesopathy formation necessary for this research. Many of these problems will be addressed in the following chapters.

Current recording criteria for MSM are generally based on the appearance of the enthesis (Dutour 1986; Hawkey 1988; Hawkey and Merbs 1995; Mariotti, *et al.* 2004, 2007; Mays, *et al.* 1999; Robb 1998; Stirland 1998; Villotte 2006). Dutour (1986) used the presence and absence of enthesopathies, whereas the majority of authors have used scoring systems based on perceived severity of the musculoskeletal stress insult. This severity is recognised as the quantity of new bone formation (bone spur(s)) or size of lytic lesions. The method developed by Hawkey (1988) also recognises roughness (described as robusticity). These expressions are given numerical values for statistical comparisons of samples. Hawkey and Merbs (1995) is the most frequently used method in bioarchaeology (Table 2.2). In this, the most commonly used recording system, the robusticity markers are said to indicate normal,

daily usage; lytic lesions are thought to indicate areas of activity-induced micro-trauma, while bone spurs are indicative of abrupt macro-trauma, *e.g.* soft tissue rupture. The diagnosis of cause and effect goes to the fundament of MSM research; and it is the aim of the research presented in the following chapters to discover the validity of such statements.

Table 2.2 The most common recording system for MSM (Hawkey and Merbs 1995).

MSM expression	Definition	Quantification of severity
"robusticity marker"	Varies between rugged marks and crests of bone	'0 = no expression, 1 = robusticity grade 1 (faint), 2 = robusticity grade 2 (moderate), 3 = robusticity grade 3 (strong)'
"stress lesion"	Varies between pitting and furrows	'0 = no expression,4 = stress lesion grade 1 (faint), 5 = stress lesion grade 2 (moderate), and 6 = stress lesion grade 3 (strong)'
"ossification exostosis"	Bone spur	Analysed separately

Quantitative approaches to enthesis recording have relied on measurement of the area of entheses (Wilczak 1998) and the relationship between MSM and cortical bone thickness (Stirland 1998). The latter technique was found to be of limited success, by the author, who found no correlation. Wilczak observed a correlation between enthesis area and age in males, but not females. Other measurements of the humerus showed no correlation. However, these are limited studies and measurement of entheses may prove to be a useful technique. Three-dimensional analysis has also been performed (Zumwalt 2005, 2006). This analysis was performed on sheep some of which were exercised and some not. No differences were found in attachment site roughness (as measured by average fractal dimensions) between the two groups, indicating that exercise did not influence attachment site roughness. This will be discussed further in Chapter 6.

Entheses, as will be discussed in detail in chapter 3, are zones of high localised stress concentration. Stress is either distributed over a larger surface area, as at the deltoid tuberosity; or over a small area mediated by two layers of fibrocartilage. The entheses of the former type are normally poorly defined and rough, whereas those of the latter

are normally very smooth and well-demarcated. These differences have not been taken into account by any of the recording methods discussed in this section (excepting Villotte 2006), making this the primary problem with all these methods. The secondary problem for this approach to the study of activity is the qualitative nature of the recording methods. Unless these qualities refer to real changes caused by musculoskeletal stress, then they are meaningless. Recording also needs to take into account the anatomy of attachment sites and must be tailored to suit it. More importantly there needs to be clinical data supporting the direct relationship between musculoskeletal stress and MSM. Such clinical data is rarely discussed in the palaeopathological literature on MSM indicating that it either does not exist or has not been referred to for either the collection or the interpretation of MSM data. Whether MSM represent many repetitions over a lifetime, a higher frequency of repetitions or greater loading per repetition is rarely discussed in the literature. However, in the occupational health literature this is an essential distinction (Luttmann, *et al.* 2003), and one that should perhaps also be made in the literature on MSM. Without such support the study of MSM is purely hypothetical. It is the aim of this thesis to address these questions.

2.3.3 Miscellaneous

This section describes less commonly used methods to determine activity-levels and occupations in bioarchaeology.

2.3.3.1 Cortical bone re-modeling

Cortical bone re-modelling is stimulated by mechanical stress (Ruff 1992, p. 54). For this reason a number of studies have attempted to relate micro-structural re-modelling to cross-sectional geometry. Ruff (1992) discussed the findings which support the presence of a positive correlation. One study (Burr, *et al.* 1990) found a greater osteon population density (suggesting more frequent bone turnover) in a Pecos Pueblo sample than in a modern North American sample. This corroborated the cross-

sectional geometric data indicating that the archaeological population were more active than the modern one.

Larsen`s (1997) discussion included more recent data indicating that males have more osteons than females, perhaps because males were more active in the population studied (a late Christian, AD 550-1450 Nubian site). This is supported by statistically significant differences in osteonal cross-sectional areas and number of intact osteons between males and females in femora, whereas no significant differences were found in the ribs (Mulhern 1998). Other experimental evidence also indicates that activity-levels influence the histology of cortical bone because of changes in osteon remodelling (Larsen 1997).

2.3.3.2 Joint surfaces

A link between the shape of the sacroiliac joint and activity levels was found in the Christ Church, Spitalfields skeletons (Molleson and Cox 1993). However, experimental research (Liebermann, *et al.* 2000) found that articular surface area is not significantly affected by mechanical loading. Articular surface area in the lower limb is affected by body mass during growth, as discussed above.

2.3.3.3 Schmorl's nodes

Schmorl's nodes are thought to be caused by herniation of the nucleus pulposus through the vertebral endplates (Apley and Solomon 1982), via fissures in the cartilaginous endplates (Faccia and WIlliams 2008). Schmorl`s nodes are defined bioarchaeologically as the result of this, *i.e.* the presence of focal lytic lesions in the vertebral body (*ibid.*). These have been linked to activities such as horse-riding (Reinhard and Wall 2002) and heavy lifting (Jurmain 1999). However, their aetiology is, as yet, unknown (but appears to be multifactorial, according to Faccia and Williams 2007) and they appear to be common (Jurmain 1999) and have been linked to development, congenital spinal defects and senescence (Faccia and Williams 2007). Clinically, they have been reported in approximately 75 percent of autopsy patients

(Apley and Solomon 1982). In the skeletal collection from St. Martin's, Birmingham, the prevalence was found to be similar to that of a pauper cemetery in London (Brickley, *et al.* 2006). If Schmorl's nodes are activity-related, then either the populations were undertaking similar tasks, or they are not occupation-specific and merely a representation of spinal activity. However, differences in frequencies of Schmorl's nodes have been found in skeletons from different time periods, with an increase associated with a period of monument building (Blau 2001). This may indicate that Schmorl's nodes, along with other indicators of occupational stress and other archaeological data can provide informative data for the interpretation of activity-levels in the past, but not specific activities. However, there is no clinical support for a link between occupational stress and Schmorl's nodes.

2.3.3.4 Fractures/Trauma

The types of fractures and trauma to be discussed in this section cover stress-induced fractures, *e.g.* avulsion fractures (Formicola, *et al.* 1990; Jurmain 1999; Knusel and Boylston 2002; Maat and Mastwijk 2000; Stirland 2000; Stirland and Waldron 1997), stress (*e.g.* interpersonal violence which may be occupation-related and repetitive stress) fractures ((Etxeberria and Herrasti 1991; Papathanasiou 2005; Solano 2006), such as spondylolysis (Arriaza 1997; Douglas, *et al.* 1997; Jurmain 1999); along with long bone bowing deformities (Stuart-MacAdam, *et al.* 1998). Fractures not caused by occupational or activity-related stress will not be considered here. However, it should be noted that it may be possible to make inferences about activity-patterns by studying fracture patterns in populations. Nevertheless, it should always be remembered that fractures can occur for a variety of reasons including underlying pathology, accidental trauma and deliberate trauma.

Avulsion fractures are thought to be caused by repetitive micro-trauma at or around the site of either an apophysis or an epiphysis. In the archaeological literature, evidence for this type of fracture has been found in the spine (Jurmain 1999; Maat and Mastwijk 2000), scapula (Stirland and Waldron 1997), humerus (Knusel and Boylston 2002), femur (Formicola, *et al.* 1990), and tibia (Stirland 2000, pp. 106-107). It has been, however, difficult to attribute specific activities to any of these lesions (Jurmain

1999); this is due to the range of different activities that involve similar limb usage. For example, a lesion often called clay-shoveller's fracture (avulsion of a portion of the spinous process (Jurmain 1999) occurs in clay-shovellers, weight-lifters, hay-pitchers and root pullers, not to mention non-activity related trauma (Jurmain 1999; Knusel, *et al.* 1996). These fractures can also be caused by acute or repetitive trauma (Jordana, *et al.* 2006). Consequently, avulsion fractures cannot be used as "stand-alone" activity indicators.

Fatigue fractures are fractures caused by repeated stress rather than direct injury and are common in some diseases, *e.g.* osteoporosis (Hayes 1991). However, they can also occur in response to "overuse" (Devas 1975). They develop as fractures in the bone structure at loads below the failure load (Panjabi and White 1978). Although these fractures can be associated with general activities, dosage of loading required to cause them is probably specific to the individual and frequency, intensity and duration of the stress.

Another form of spinal fatigue fracture; spondylolysis, is the result of fracture of the neural arch, in which there may be a congenital weakness. This fracture is, in fact, quite common in a modern population; five percent of five-year-olds have this condition and six percent of adults (Dandy and Edwards 1999, p. 444). Mays (2007) has also observed spondylolysis in subadults from archaeological populations. This fracture does not occur in non-human primates or in humans who have never walked and is likely to be related to erect posture (Jurmain 1999). Some authors have tried to relate this lesion to activities (Capasso *et al.* 1999), but in the clinical literature it has been linked to a large number of activities that relating it to one specific activity is not possible (Jurmain 1999). This lesion has been found in many populations around the world and, although prevalence rates do seem to differ (Arriaza 1997; Waldron 1991), it is uncertain how much of this relates to trauma and how much to congenital weakness (Arriaza 1997; Merbs 1996; Waldron 1991). Other spinal fractures have also been associated with activity. These include Jefferson fracture (two or more fractures of the arches of the atlas), Porter's neck of Levy (fractures and forward dislocation of cervical vertebrae), along with general fractures of the cervical spine which are all associated with carrying loads on the head (Capasso *et al.* 1999).

Bowing deformities of long bones have also been postulated as being activity-induced (Stuart-MacAdam, *et al.* 1998). It is known, from modern clinical literature that compressive or tangential forces applied to the bones can cause bowing deformities of long bones, even in adults (but it is unclear whether these forces have to be extreme, *i.e.* occurring in relation to industrial accidents rather than long-term limb use). Unfortunately, even if these changes were definitely related to occupational stress, they are difficult to distinguish from other causes, *e.g.* metabolic diseases, and acidic soil conditions. Consequently, they are probably not of use to palaeopathologists as indicators of activity.

Myositis ossificans can be a complication of fractures or it occurs because of other trauma (Ortner 2003a; Resnick and Niwayama 1995e). Myositis ossificans leads to the calcification of muscle, caused by a haematoma, which can cause osteoblasts to move into the muscle (DeGroot 1998; Ortner 2003a; Resnick and Niwayama 1995e). It can also occur because of a rare autosomal dominant disorder (Pattekar 2003), but this will not be discussed in the present context. Such calcifications, when joined to the bone, have been found in the archaeological record (Aufderheide and Rodríguez-Martín 1998; Mann 1993; Ortner 2003a). Mann (1993) found evidence of this in femora from St. Bride's Church, Fleet Street, London, a population which has ties with the shoemaking industry. It was postulated that strapping the shoes to their thighs during the manufacturing process may have caused enough trauma to lead to this condition.

2.3.3.5 Disease

Occupational diseases can be caused by chemical pollutants, such as heavy metals (WHO?). Current pollution levels of copper and lead in some areas of the world, notably Jordan, were created by prehistoric metal use (Pyatt and Grattan 2001). This has been traced in skeletons using mass spectrometry (Oakberg, *et al.* 2000). However, no pathognomonic signs of these diseases can be found on skeletons. Similarly, elevated levels of lead in alluvial sediments have been found from the 9th to the 13th centuries in York, which reflect river contamination from mining (in the North Yorkshire dales), smelting, and use and disposal of lead based products

(Hudson-Edwards, *et al.* 1999). However, it is unlikely that any of the symptoms or signs of lead poisoning (plumbism) would be obvious in the skeleton (Berkow 1982). In contrast, yellow phosphorus, used in the match industry in the 19th century, is known to cause necrosis of the mandible (Capasso *et al.* 1999). Industry is also related to sinusitis frequencies in archaeological skeletal samples (Roberts 2007). Skeletons from rural sample, higher status samples, and hunter-gatherers had lower sinusitis frequencies than those buried at St. Helen-on-the-Walls, York, and Fishergate House, York. Both of these samples have been linked with urban industrial sites.

Bone forming (as defined by Rogers *et al.* 1997) and DISH have been found to be more common in monastic compared to lay cemeteries (Kacki and Villotte 2006; Rogers, *et al.* 1997; Rogers and Waldron 2001). It was also found in a Lithuanian sample, where it was linked to high status (Jankauskas 2003). However, as the aetiology of the disease is unknown [for example it may be linked to senescence (Vidal 2000)], it cannot be considered an occupational disease. This disease will be discussed further in Chapter 5. Sinusitis has also been linked to occupation by Roberts (2007).

2.3.3.6 Non-Metric Traits

Non-metric traits are normal anatomical features of unknown aetiology occurring in various parts of the skeleton. Cranial non-metric traits are not considered in this section for two reasons, firstly they have been linked to specific genes (Hauser and de Stefano 1989) and secondly because the skull is only rarely affected by activity (Kennedy 1989). Some postcranial non-metric traits, on the other hand, have been linked to activity, because they are either near articular surfaces or at entheses (Boulle 2000, 2001a, b; Capasso, *et al.* 1999; Douglas, *et al.* 1997; Hawkey and Street 1992; Henderson 2002; Jennings, *et al.* 2004; Kovacik, *et al.* 2004; Lovell and Dublenko 1999; Mafart 2005; Malim and Hines 1998; Molleson 1994; Trinkaus 1978; Ubelaker 1979; Ullinger, *et al.* 2004), see Table 2.3. Unlike other MOS, none of these postcranial non-metric traits have been studied in clinical contexts, primarily because they are asymptomatic and non-lethal. Consequently, all studies have come from anatomical and anthropological literature. Aetiology is, therefore, difficult to assess.

Table 2.3 Example of non-metric traits and the activities that have been associated with their presence.

Non-metric trait	Location	Association with activity (reference)
Acetabular crease	Notch of groove on acetabular margin of the acetabulum	Childhood biomechanical stress (Mafart 2005)
Allen's fossa	Anterior aspect of femoral neck	Kneeling and genuflection (Jennings *et al.* 2004); squatting, or hyperextension (*e.g.* mountaineering) (Capasso *et al.* 1999)
Poirier's facet	Anterior aspect of femoral neck	Possible extreme extensions (Capasso *et al.* 1999)
Plaque (femur)	Anterior aspect of femoral neck	Deep flexion of the knee, as in prayer/genuflection (Jennings *et al.* 2004; Kovacik *et al.* 2004)
Exostosis in trochanteric fossa	Trochanteric fossa of femur	Kayaking with legs extended (Capasso *et al.* 1999)
Squatting facets	Articular facets on dorsal region of talar neck, with reciprocal facets on anterior aspect of distal end of tibia	Hyperdorsiflexion of the ankle as occurring in squatting (Boulle 2001a; 2001b), genuflection (Ullinger *et al.* 2004), squatting (Capasso *et al.* 1999)

2.3.4 Markers of Occupational Stress (MOS): Conclusions

It is clear that there is almost no clinical backing for many of the claims that have been made regarding the relationship between these markers and occupational stress. However, there is considerable palaeopathological literature and almost at almost every conference more is published. For this reason studying the relationship between these markers and occupational stress in relation to clinical literature is becoming increasingly urgent. This is especially the case for MSM, for which the direct link between occupational stress and enthesopathy formation seems highly logical and almost deductive. However, it is important to understand the multifactorial nature of MSM, DJD and the other markers discussed.

2.4 Summary and Conclusions

To summarise, one aspect stands out as affecting the validity of all the methods used by bioarchaeologists to record activity and occupation-related stress: this is the problem of a lack of clinical evidence proving links between cause and effect. In those cases where physical stress is a cause of these changes, there is little evidence to link them to specific activities. Individual variation and the multifactorial nature of both DJD and MSM aetiology makes these especially difficult to use to relate to specific tasks. The lack of anatomical understanding of entheses also makes the recording and the interpretation of the data at present unreliable. However, the relationship between physical activity and entheses is closer than for many of the other methods because of their direct link with movement-related soft tissues. For this reason they are likely to outperform other methods, such as DJD analysis and for this reason further research into them is necessary.

Chapter 3. The nature and relevance of the anatomy of the soft tissue attachment sites to the skeleton

3.1 Introduction

An enthesis is the junction between soft tissue and bone. It is important to understand these anatomical features when recording enthesopathies because the normal appearance of the enthesis must be taken into account before recording begins. As will be seen below, the normal appearance of attachment sites is variable, but this is not reflected in the recording methods currently in use (*e.g.* the Hawkey and Merbs 1995 method), as discussed in the previous chapter. Understanding the anatomical reasons for enthesopathy formation is also essential for their recording and interpretation. All aetiological factors and factors influencing their appearance must be taken into account for the production of a recording method which reflects their true characteristics. Consequently, a discussion of aetiological factors is also presented in this chapter.

Anatomists have studied entheses since the 17th century (Weiler, *et al.* 2006). Initially, the differences in anatomy of the entheses (to be discussed in detail below) were attributed to developmental factors (Woo and Young 1991). However, the importance of biomechanics has been stressed recently (Benjamin, *et al.* 2002) and this has led to a change in terminology. This chapter will use the terminology defined by Benjamin and colleagues (2002), which will be discussed below.

3.2 Anatomy of soft tissue structures attaching to bone

Tendons have the primary role of transferring muscle pull to a bone, but they also have three subsidiary roles: to allow the muscle to be at a distance from the joint; to allow force to be transmitted around corners; and to store energy (Currey 2002). They are frequently attached to the bone close to the joint upon which they act, allowing the

speed of their action on the joint to be maximised (Benjamin and Ralphs 1996; Currey 2002). Elongation of the tendon is not desired (Gelberman, *et al.* 1988) because this would require the muscle to shorten further. However, tendons can stretch and this ability is used to store energy (Currey 2002). Where stretch is less desirable the tendon is thicker, which decreases its elasticity.

Tendons are white, fibrous cords of varying shapes, consisting mainly of longitudinally oriented collagen fibres (Gray 1974; Stevens and Lowe 1997). Not all muscles have tendons (*e.g.* the insertion of the deltoid) and some have multiple tendons (*e.g.* the origin of the *biceps brachii*). Tendons themselves can be either thin or rounded; often this depends on the function of the muscle associated with the tendon, for example, the tendons of the wrist are rounded enabling them to fit into the space available (Benjamin, *et al.* 2002).

Tendon strength is related to its thickness (Elliott 1967). Tendons have a greater tensile strength than the muscles to which they belong; consequently, muscle ruptures are more common than tendon injury (see Chapter 4 for a discussion of tendon injury) ((Benjamin and Ralphs 1996). Tendons have time and history dependent visco-elastic properties (Gelberman, *et al.* 1988). This means that stress-strain curves are influenced by previous loading patterns and that rest is required for them to return to normal (*ibid.*). Proteoglycans, which are macromolecules composed of polysaccharides and polypeptides, and water contribute to these properties making *in vitro* stress testing of tendons difficult as *in vivo* conditions cannot be properly maintained post-mortem (*ibid.*).

Blood supply in tendons and ligaments is poor, but is thought to increase in response to exercise and during healing processes (Benjamin and Ralphs 1997). The blood supply to tendons comes through the myotendinous junction and through the bone in fibrous entheses (see Section 3.3). In fibrocartilaginous entheses the vascular network of tendons does not continue into the enthesis, but ends in a blind alley of capillary loops (Dörfl 1969a). However, around the periphery of these insertions the vessels can cross into the bone (Dörfl 1969b). Tendons can also be avascular in other regions where they are subjected to stress, or friction (Benjamin and Ralphs 1997). Nutrients are distributed in the tendon via the bloodstream and from the surrounding synovial

sheaths (*ibid.*). According to Gelberman *et al.* (1988). this occurs by means of a combination of perfusion and diffusion. Perfusion occurs in the vascular zones, whereas diffusion occurs in the avascular areas. Diffusion has been found to be faster and a more effective means of distributing nutrients within a tendon and is an important factor in tendon healing (see Chapter 4, Section 2.1)

Tendon and ligament cells have attracted little attention, as they are often considered less important than the collagenous extra-cellular matrix, which comprises 70-80 percent of the dry weight of the tendon (Benjamin and Ralphs 1997). The cells themselves are fibroblasts, although fibrocartilage cells do occur in those areas under compression. The cells communicate via gap junctions and cell processes. It has been hypothesised that these are the means for sensing and adapting to stresses both in the tendon and within the enthesis (Banes, *et al.* 1995).

The collagenous content is, according to Benjamin and Ralphs (1997), composed, primarily, of collagen type I, but other types of collagen associated with fibrillogenesis (*e.g.* types IX, XII, and XIV), other fibrillar collagens (types III and V) and collagen type VI, which has an unknown function (Linsenmayer 1991) also occur. Proteoglycans are also present, some of which are associated with fibril formation: *i.e.* they are thought to help to control fibril diameter and rate of formation. Proteoglycans are also associated with the binding of water, which is important for the resistance of compressive forces.

Ligaments attach bone to bone, for example the talo-calcaneal ligament which connects the talus to the calcaneus. Ligaments can either be capsular or accessory. Capsular ligaments are those that appear as local thickenings in the joint capsule (Benjamin and Ralphs 1997). Accessory ligaments are those that are separate from the joint capsule, but they can occur either within the capsule or outside it, according to these authors. In general their role is to stabilise the joint thereby protecting it from excessive or abnormal movement (*ibid.*). They also have a neurosensory role, to provide feedback from the joint to the brain (Franck, *et al.* 1988).

Ligament biomechanics are dependent on many factors, for example collagen fibre orientation, proportions of other constituents (such as water) and their geometric

properties (*e.g.* cross-section and thickness) (Franck, *et al.* 1988). Ligaments, like tendons, respond to mechanical stress. In ligaments this is achieved by changes in weight and size (McGonagle, *et al.* 1999).

3.3 Anatomy of the enthesis

An enthesis is the attachment of tendon, ligament, aponeurosis, meniscus or the joint capsule to bone (Benjamin and McGonagle 2001; François, *et al.* 2001). Some authors (Fournié 1993) think that this should be extended to include the intervertebral disc in its entirety, the sacroiliac joint, the pubic symphysis and the manubriosternal junction. The extension of the definition of enthesis is based on the theory that all similar structures that can be involved in the seronegative spondyloarthropathies should be called entheses (François, *et al.* 2001). This chapter follows the conventional usage of the term to avoid confusion with the majority of medical texts, *i.e.* not including these other structures involved in seronegative spondyloarthropathy. The anatomy of entheses is governed by many factors: mechanical requirements (Benjamin, *et al.* 2002; Benjamin, *et al.* 1992; Benjamin and Ralphs 1996; Benjamin and Ralphs 1998; Biewener, *et al.* 1996; Clark and Stechschulte 1998; Cooper and Misol 1970; Haines and Mohuiddin 1968; Hems and Tillmann 2000; Hoyte and Enlow 1966; Kumai and Benjamin 2001; Milz, *et al.* 1998; Milz, *et al.* 2002; Milz, *et al.* 2001; Moriggl, *et al.* 2001; Waggett, *et al.* 1998), developmental constraints (Benjamin, *et al.* 1992; Dörfl 1980a, b; Hoyte and Enlow 1966; Woo and Young 1991), and individual variation (Benjamin, *et al.* 1991; Benjamin and Ralphs 1998). These factors will be discussed below.

Some authors (Benjamin and McGonagle 2001) have proposed that there is an "enthesis organ". This is an ultra-structure of soft tissue and bone adaptation in the region of the actual attachment site that is functionally related to the attachment. These structures are not, necessarily, visible on skeletal remains. The concept is thought by Benjamin and McGonagle (*ibid.*) to be useful when considering enthesopathy-forming diseases which also seem to affect these structures (McGonagle, *et al.* 2002a; McGonagle, *et al.* 2001). Of particular importance in this

respect are the enthesis organs found in the hands and feet, as these are thought to be affected in psoriatic arthritis (Chapter 5) and changes to them are used as an indicator of disease when recording skeletons from archaeological sites (Chapters 5 and 6). In the interphalangeal joints, tendons and ligaments replace the joint capsule found in most synovial joints, according to Benjamin and McGonagle (2001). These authors describe the enthesis organ in the interphalangeal joints. This comprises the digital extensor tendon enthesis, '*the sesamoid fibrocartilage in the deep part of the tendon*' (*ibid.* p. 508) (when flexed, the sesamoid fibrocartilage articulates with the head of the phalanx) and '*the synovial recess of the joint cavity*' (*ibid.*). However, other authors (Gosling, *et al.* 2002; Sahin and Wilhelmi 2003) discuss the interphalangeal joint capsule, indicating that this joint capsule is no different to those surrounding other synovial joints. However, this is probably only a matter of definition, rather than a difference in anatomy.

Wrap-around regions of tendons are similar to enthesis organs in that both the tendon and bone are covered in a layer of fibrocartilage (Benjamin and Ralphs 1997). Wrap-around tendons and ligaments have regions where the soft-tissue is wrapped around one or more bone pulleys (*e.g.* the malleoli the tibia and fibula, and the dens of the atlas) or a fibrous band (*e.g.* the extensor retinacula in the feet) (*ibid.*). These structures allow the force of the muscle to be transferred around a corner. In wrap-around tendons the compressive force at the pulley on the tendon is approximately '*twice the tension generated in the tendon multiplied by half the sine of the angle through which it changes its direction*' (*ibid.*, p. 1140). Experiments have demonstrated that fibrocartilage in the tendon or ligament is only maintained while the area of compression is present, so if a tendon is moved to bypass a bone pulley the fibrocartilaginous regions will disappear.

3.3.1 Mechanical requirements

The functions of an enthesis and the mechanical requirements placed on it have significant influences on enthesis morphology. As stated in the introduction, the function of an enthesis is to join two disparate materials together, while enabling the

tendon or ligament to act on the bone. Mechanically, this should mean that stress is concentrated at the interface of the two materials because of their different mechanical properties (Benjamin, *et al.* 2002). It is thought that the structure of an enthesis solves this problem by dissipating the stress into the tendon and bone and away from the interface itself (*ibid.*). This is achieved by a number of mechanisms, discussed below. Additional stress dissipation is provided by the splaying out of collagen fibres before they enter the enthesis (Benjamin and Ralphs 1999). This means that the dimensions of the enthesis are often greater than the tendon at its midsubstance.

Not only should stress be concentrated at the interface between the two materials, but tendons and ligaments should also transmit tensile loads to bone. However, some authors (Clark and Stechschulte 1998) think that bone is weak in tension, whereas other authors (Hoyte and Enlow 1966) suggest that tension in bone stimulates bone remodelling, but that this is a long-term adjustment. Other authors (Benjamin, *et al.* 1992) have found that stress and movement affect the morphology of entheses and determine levels of fibrocartilage found at them.

Fibrocartilage at entheses, enthesis organs and other sites covered in fibrocartilage, *e.g.* wrap-around-tendons (see above), allows gradual bending of the tendon or ligament as a joint moves (these entheses are found at epiphyses, close to the joint upon which they act), thereby reducing stress at the interface (Benjamin and Ralphs 1998; Hems and Tillmann 2000; Moriggl, *et al.* 2001). It also stops the tendon or ligament narrowing at the enthesis under tension (Benjamin and Ralphs 1996; Benjamin and Ralphs 1998; Hems and Tillmann 2000). There is also a gradual change in mechanical properties from tendon or ligament to bone (Rufai 1995; Waggett, *et al.* 1998). Fibrocartilage is formed metaplastically and this too has mechanical advantages because the collagen fibres of the tendon or ligament are continued into the metaplastically formed fibrocartilage (Haines and Mohuiddin 1968). It is possible that these fibres act like trabeculae in bone distributing loading away from a single point.

Compression has also been suggested as a possible reason for fibrocartilage presence in entheses (Benjamin and Ralphs 1998; Milz, *et al.* 2001; Moriggl, *et al.* 2001; Waggett, *et al.* 1998). The role of compression in the formation of fibrocartilage has

been demonstrated surgically within tendons themselves. Benjamin and Ralphs (1998) described an experiment demonstrating this. A tendon in a rabbit was surgically moved into a position in which it was wrapped around a bony pulley. Conversely, a wrap-around tendon was converted into a direct one in the same rabbit. Fibrocartilage disappeared from the tendon that had been unwrapped and appeared in the one that had been wrapped, but only on the side subject to compression, not on the side subject to shear. It is unclear which factors are most important in the formation of fibrocartilage, but it does seem plausible to assume, from the evidence above, that mechanical factors are the primary cause.

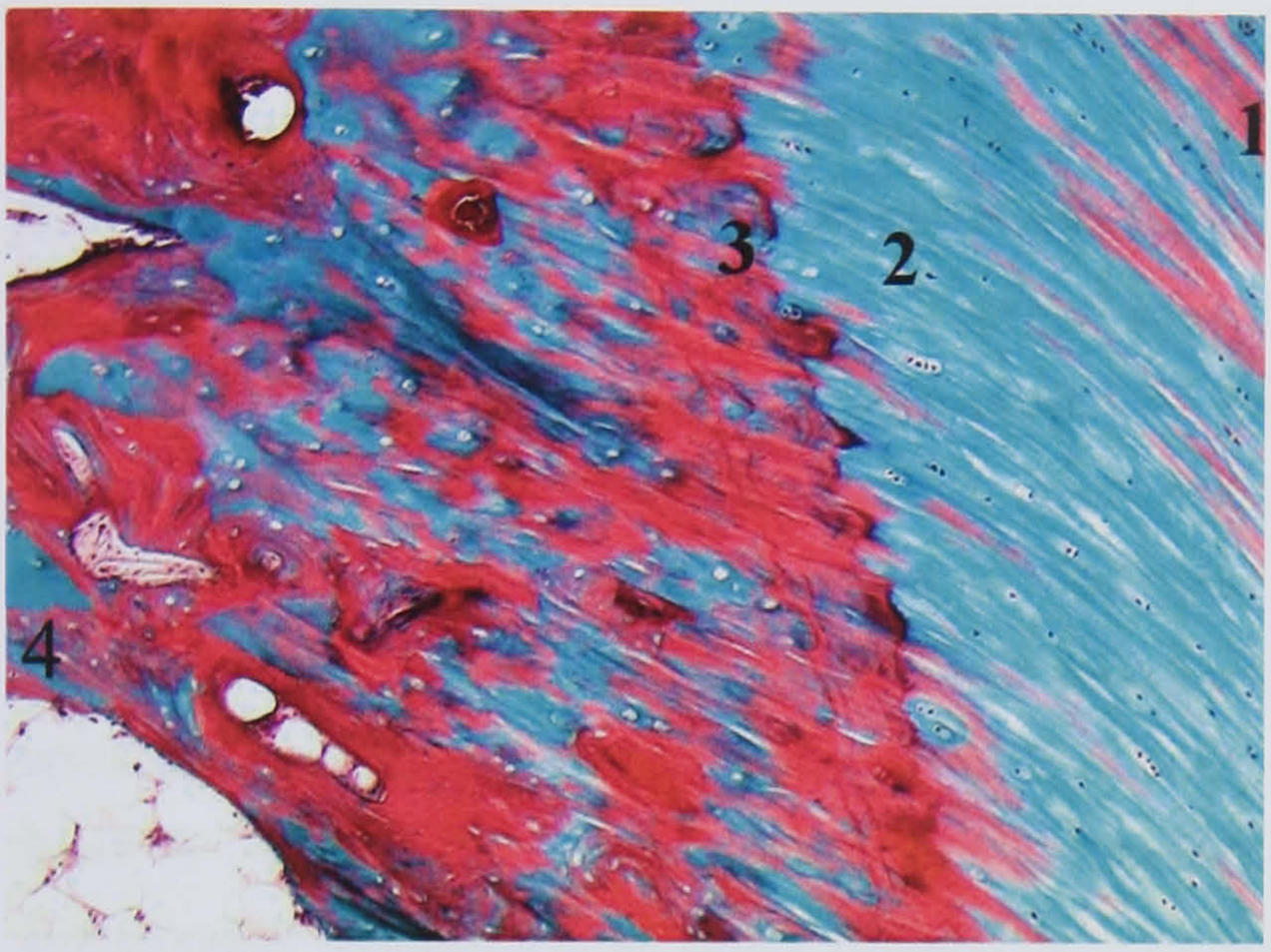
Presumably, fibrous entheses also avoid the problems of stress concentration at the tendon-bone interface by a gradual change in mechanical properties (Cooper and Misol 1970). These attachments also occur over a relatively large area, allowing the force to be dissipated (Benjamin, *et al.* 2002). Little more has been stated in the literature regarding mechanical considerations at fibrous entheses; on the other hand, fibrocartilaginous entheses have been thoroughly described in the literature, primarily due to the range of injuries and diseases that affect these attachment sites (see Chapter 5).

Mechanical forces also affect trabeculae and bone collagen orientation in the underlying bone (Biewener, *et al.* 1996; Clark and Stechschulte 1998). Biewener *et al.* (1996) found that the trabeculae in sheep and poteroo (a small marsupial) calcanei were oriented along the line of principal strain in the cortical surface. Primarily, this was related to compressive and tensile loading. Clark and Stechschulte (1998) found that bone collagen surrounding the marrow spaces in patellae was also aligned, in this case longitudinally in relation to tensile loads. It is clear from this section that mechanical loading patterns affect the enthesis as well as the bone underlying this region (and indeed bone in general). This fact, combined with Wolff's law, indicates that bone is affected and changed by the loading patterns that occur throughout life.

3.3.2 Fibrocartilaginous entheses

As stated above, fibrocartilaginous entheses occur at attachment sites on "*epiphyses of long bones or to the short bones of the tarsus or carpus*" (Benjamin and Ralphs 1998, p. 488). These entheses have a risk of degenerative changes because the angle of the tendon at the insertion changes considerably during joint movement (Benjamin and Ralphs 1998). Therefore, extra protection is required to avoid these changes; nevertheless, these entheses are more commonly associated with injury than those on the diaphysis of the bone (Benjamin, *et al.* 2002). These entheses have four distinct layers or zones; these are tendon or ligament, unmineralised fibrocartilage, mineralised fibrocartilage and bone (Benjamin, *et al.* 2002; Benjamin, *et al.* 1992; Benjamin and Ralphs 1998; Clark and Stechschulte 1998; Cooper and Misol 1970; Niyibizi, *et al.* 1996) see Figure 3.1. Calcified cartilage is called "chondroid bone" (Beresford 1981); this terminology will not be used to avoid confusion with normal terminology. The structure of tendon and ligament has been outlined above and that of bone will be described in section 4; consequently, this section will focus on the two zones of fibrocartilage: unmineralised and mineralised fibrocartilage.

Figure 3.1 Fibrocartilaginous enthesis, demonstrating the four tissue zones. Zone 1 tendon, zone 2 unmineralised fibrocartilage, zone 3 mineralised fibrocartilage and zone 4 bone. The tidemark is between zones 2 and 3. Figure courtesy of Prof. M. Benjamin.



The zone of unmineralised fibrocartilage consists of the same collagen bundles found in tendons and ligaments. Cooper and Misol (1970) demonstrated that the fibrocartilage itself lay in lacunae between the rows of collagen fibres (note that this study involved dogs, not humans). The collagen fibres and elastic fibres of the tendon or ligament continued into the zone of unmineralised fibrocartilage with little change to proportion or direction. The fibroblasts of the tendon or ligament gradually changed structure and became chondrocytes, and many of these cells arranged themselves in pairs or rows. These cells lay in lacunae that extended around the cells for one to two micrometers, and these lacunae also contain collagen fibrils as well as electron dense granules, some of which attached to the collagen fibrils (*ibid.*).

Other authors (Benjamin and Ralphs 1999) have noted that the angle of incidence of the collagen fibres does change in the zone of unmineralised fibrocartilage so that the fibres are approaching the tidemark (see below) at approximately ninety degrees. These authors hypothesise that this has the effect of protecting the actual join of the

tissues by removing bending stresses away from the interfaces between cartilages and mineralised fibrocartilage and bone.

Below this zone of unmineralised fibrocartilage is a region known as a "*tidemark*" (see Figure 3.1) (Benjamin, *et al.* 2002; Benjamin and Ralphs 1998). This region is the boundary between soft and hard tissues [and is the point at which soft tissues fall away after maceration, according to Benjamin and Ralphs (1998) and François *et al.* (2001)]. It is not only similar to the tidemark found in articular cartilages (Benjamin *et al.* 2002), but can be continuous with it in entheses close to synovial joints, for example the supraspinatus insertion. It is composed of dense granular material that is basophilic, meaning that this region is acidic (Ham 1957). Collagen fibres cross this region at right angles to it (Benjamin *et al.* 2002) and continue into the zone of mineralised fibrocartilage (see below). Unlike collagen fibres, blood vessels do not cross this point (Benjamin and Ralphs 1998; François, *et al.* 2001). The tidemark itself is straight, but can be duplicated, particularly in individuals with an enthesopathy (Benjamin *et al.* 2002). Because the tidemark is straight and not crossed by blood vessels, these types of entheses appear as smooth well-defined zones on skeletal remains (Benjamin, *et al.* 2002; Benjamin and Ralphs 1999).

Collagen fibres continue into the region of mineralised fibrocartilage (Cooper and Misol 1970). Cooper and Misol (1970), in their study of dog patella tendons, found two sections of mineralised fibrocartilage. In the upper section of this zone, crystals were found in and between the collagen fibrils. In the deeper zone mineral extended into the collagen fibrils themselves, but no crystals (one assumes these are hydroxyapatite, as this is the composition of bone) were found in the elastic fibres. The cartilage cells found in the layer of unmineralised fibrocartilage had degenerated in some cases, but some remained active even though they were surrounded by mineral (Cooper and Misol 1970).

The junction between mineralised fibrocartilage and bone is a complex zone of interdigitation between the two tissues, very similar to the join between jigsaw pieces (Benjamin, *et al.* 2000). This increases surface contact area, thereby spreading the load, and provides resistance to shear (Benjamin and Ralphs 1999).

Some entheses have areas which lack the unmineralised and mineralised fibrocartilage (Benjamin and Ralphs 1999). In general it is found that the deepest zones of fibrocartilage are those nearest the joint upon which the tendon acts (*ibid.*). This is probably because these regions are subject to greater compressive stress. However, modelling of these areas is required to fully understand stress distribution in relation to fibrocartilage content.

Biochemical analytical techniques have shed further light on the structure of entheses and related fibrocartilaginous regions. The work that has been undertaken suggests that there are a number of different types of collagen and proteoglycans present at the enthesis (Hems and Tillmann 2000; Niyibizi, *et al.* 1996; Waggett, *et al.* 1998). These chemicals have different roles and different biomechanical properties (Thomopoulos, *et al.* 2003) and have been found in differing quantities in different individuals and at different sites (Waggett, *et al.* 1998). Collagen is a protein that is found in the extracellular matrix of connective tissues and has a primarily structural role (Woodhead-Galloway 1980). These proteins are built up of chains of amino acids and the differences in these chains determine the type of collagen (Linsenmayer 1991). Proteoglycans consist of a core protein covalently bonded to one or more polysaccharides (called glycosaminoglycans) and they are found in all connective tissues (Lodish, *et al.* 1995).

The primary collagens found at Achilles tendon entheses (Waggett, *et al.* 1998) were types I and types III, their principle function being to promote tensile strength (*ibid.*). Type II collagen was also found in the fibrocartilage; this is in keeping with the observation that fibrocartilage is a tissue mid-way between tendon (primarily type I collagen) and hyaline cartilage (primarily type II collagen) (Waggett, *et al.* 1998). Other types of collagen found were type V collagen, a regulator of fibril diameter in type I collagen (Waggett, *et al.* 1998) and type VI collagen. One research group found type X and type XI collagens at the enthesis of bovine medial collateral ligaments, but no other paper confirms the presence of the latter (Niyibizi, *et al.* 1996). Type X collagen, on the other hand, has been found on more than one occasion (Benjamin, *et al.* 2002; Niyibizi, *et al.* 1996; Thomopoulos, *et al.* 2003); it might have the role of forming scaffolding for mineralization to occur (Niyibizi *et al.* 1996). Type IX and type XII were found in the supraspinatus tendon insertion of rats (Thomopoulos, *et al.*

2003), the former at the bony section of the insertion and the latter at both the tendon and bone sections of the insertion (*ibid.*).

Waggett and colleagues (1998) found the proteoglycans; biglycan, lumican, aggrecan, fibromodulin, decorin, and versican at the insertion of the Achilles tendon. These molecules all regulate the structure of the extracellular matrix. Decorin, lumican, and fibromodulin enable collagen fibril formation (Waggett, *et al.* 1998). They propose that biglycan might bind growth factors and is characteristic of foetal tendons that become fibrocartilaginous. Whereas, versican may regulate cell motility, growth and differentiation, aggrecan attracts water, due to its charged glycosaminoglycan side chains, thereby enabling it to resist compressive forces, because liquids are not easily compressed (Benjamin, *et al.* 2002). It has also been found in other regions where the body needs to be able to resist compressive forces, notably articular cartilage and wrap-around-tendons (Benjamin, *et al.* 2002; Waggett, *et al.* 1998).

Thomopoulos, *et al.* (2003) studied the biochemistry of the insertion of the rat supraspinatus tendon both quantitatively and qualitatively; histological, geometric and biomechanical assays were used, *i.e.* mRNA levels were measured as opposed to the proteins themselves. Two sections of the points on the insertion were studied, the tendon and the bone. The fibrocartilaginous zones in between were not used. The authors found that the tendon zone consisted of collagen types I, III, and XII and the proteoglycans, decorin and biglycan. The collagen fibres themselves were more organised in this zone than in the bony region. This zone also had better elastic and viscous properties. Effectively, this means that the tendon zone can be under greater and more prolonged tension than the bony end of the insertion (*ibid.* p. 417); perhaps this explains why avulsion injuries occur within the bone (Benjamin, *et al.* 2002; Benjamin, *et al.* 1992; Clark and Stechschulte 1998; Kumai, *et al.* 2002) (see Chapter 4). It should be noted at this point that the biomechanical properties of the enthesis were only determined under tension, not under compression, a force which is important at the bony end of the enthesis. The bony zone of the enthesis was composed of collagen types I, II, III, IX, X and XII as well as the proteoglycan aggrecan. The collagen fibres themselves were less organised and consequently better at transmitting the multidirectional forces that probably occur at this point (*ibid.* p.416). The role of the proteoglycans is not well understood, but clearly these

molecules, in combination with the different collagen types in the different zones, alter the viscoelastic properties of the material, thus changing its biomechanical character.

3.3.2.1 Development

The development of fibrocartilaginous entheses (specifically the Achilles tendon attachment to the calcaneus) in rats has been documented by Benjamin *et al.* (2000). At the age of 2 weeks after birth the tendon is attached to the cartilage rudiment of the calcaneus, as the ossification of the calcaneus had not reached the enthesis. There was, however, evidence of fibrocartilage formation in the distal portion of the tendon, and it is probable, according to the authors, that this was the basis for the entheseal fibrocartilage. At 3 weeks the cartilage below the attachment site had hypertrophied and blood vessels were invading the chondrocyte lacunae. At 4 weeks, all the original cartilage in the cartilage rudiment had been replaced by bone. Fibrocartilage cells were present in the tendon at its attachment and the vascular bone had formed an interface with the uncalcified fibrocartilage. This led to vascular invasion of the Achilles tendon and the plantar aponeurosis via the rows of fibrocartilage cells. At 7 weeks, large capillaries were found to have invaded the enthesis from the bone marrow, and these threw off smaller blood vessels which invaded several layers of fibrocartilage cells. Immunolabelling of 2- and 3-month old rats indicated that the capillaries that were extending into the fibrocartilage were part of a larger network present in the bone marrow.

The development of fibrocartilaginous entheses has also been studied in immature rabbits. The enthesis of the medial collateral ligament on the femur was studied at 2, 21, 49, and 60 days (Hurov 1986). In the first stage (2 days) the attachment was to the perichondrium, in stage 2 (21 days) to the perichondrium at the fibrocartilage, and in the third stage (49 days) chondroid bone (i.e. calcified cartilage) was also found. In the final stage, at 60 days, the attachment was via the periosteum, chondroid bone and lamellar bone. It is understood that 60 days does not represent the final growth stage of a rabbit, but that the stages studied occurred during the time of most rapid growth

in the hind limb (*ibid.*). New Zealand white rabbits (the breed studied by Hurov) have fully fused distal epiphyses at around 6 months of age and the proximal ends at around 10 months (Gibb, *et al.* 1985).

Fibrocartilage at entheses represents cartilage that remains un-eroded after endochondral ossification during growth (Benjamin and Ralphs 1999). As growth continues, this cartilage rudiment is removed on the bony side (François, *et al.* 2001) and new fibrocartilage develops by metaplasia of fibrous connective tissue in the tendon/ligament (Benjamin and Ralphs 1999). This probably develops in response to mechanical stimulation (*ibid.*). The metaplastic origin explains why there are differing quantities of fibrocartilage at different entheses and how fibrocartilage can re-appear after surgical repairs (*ibid.*).

The evidence to support this theory of development comes from the immunolabelling for types I and II collagen during the stages of development of rats (*ibid.*). New fibrocartilage develops by metaplasia on the ligament side of the enthesis and old fibrocartilage is removed on the bone side by osteoclastic erosion (*ibid.*). Therefore, the enthesis fibrocartilage acts as a growth plate, and allows for the growth of the epiphysis. Tendons do not grow considerably in length at entheses (*ibid.*), but do at the myotendinous junction (Benjamin and Ralphs 1995).

The presence of a tidemark is age-related and most typical of mature animals (Benjamin and Ralphs 1998). However, the interdigitations between calcified fibrocartilage and bone are probably established during puberty by the tensile loading of the soft tissue (Benjamin and Ralphs 1999). The size of this zone develops beyond puberty where there is motion at the hard-soft tissue interface.

3.3.3 Fibrous entheses

There is significantly less information regarding fibrous entheses because these entheses are less prone to overuse injuries. However, the fibrous entheses are those that attach some of the strongest muscles in the body to bone, *e.g.* the deltoid

(Benjamin, *et al.* 2002). In general, this type of enthesis occurs on the diaphyses (Benjamin, *et al.* 2002; Hems and Tillmann 2000) and metaphysis (Benjamin and Ralphs 1997) of long bones. Although many fibrocartilaginous entheses also have fibrous zones (Benjamin *et al.* 2002), it has been proposed that instead of thinking of entheses as either fibrous or fibrocartilaginous, they should be considered as part of a spectrum ranging between these two extremes (Milz, *et al.* 2001).

Fibrous entheses are characterised by Sharpey's fibres. These are fibres, probably collagen fibres (Benjamin, *et al.* 2002; Cooper and Misol 1970), which anchor the tendon to the bone, by being surrounded by bone, at the bony end ((François, *et al.* 2001). It should be noted, however, that there are many different uses of the term "Sharpey's fibres", and some authors even apply them to the collagen fibres that run through the fibrocartilaginous enthesis (Benjamin, *et al.* 2002; Cooper and Misol 1970). As the terminology used in this review follows modern (Benjamin, *et al.* 2002; Benjamin and McGonagle 2001; Benjamin, *et al.* 1992; Benjamin and Ralphs 1995; Benjamin and Ralphs 1996; Benjamin and Ralphs 1998; Kumai and Benjamin 2001; Kumai, *et al.* 2002; Milz, *et al.* 1998; Milz, *et al.* 2002; Milz, *et al.* 2001; Moriggl, *et al.* 2001; Rufai 1995; Waggett, *et al.* 1998); this term will be restricted to fibrous entheses.

Fibrous entheses can attach either directly to bone, or via periosteum (Benjamin, *et al.* 2002; Hems and Tillmann 2000). The latter enables force to be spread over a larger area, thus dissipating the stresses more readily (Benjamin, *et al.* 2002). However, these also limit the amount a tendon or ligament can stretch and, consequently, the tendons or ligaments themselves are short. Fibrous periosteal attachments are also found where tendons are absent; in these cases the muscle attaches to the bone via the periosteum (*ibid.*). Sharpey's fibres also attach periosteum to bone; in this case they are less densely packed than those that attach tendon or ligament to bone (François, *et al.* 2001). For this reason the bone at periosteally inserting fibrous entheses does not have the striated character of fibrous tendon or ligament attachments (*ibid.*). In entheses where muscles attach directly to the periosteum the vessels of the external adventitial layer supply both the periosteum and enthesis (Dörfl 1969b). The enthesis is connected with the bone vessels by means of periosteal vessels (*ibid.*). Fibrous bony entheses, on the other hand, occur where the tendon attaches directly to the bone,

without an intermediate tissue ((Benjamin, *et al.* 2002; Hems and Tillmann 2000). For a description of the characteristics of the underlying bone see Section 3.4. Fibrous periosteal attachments can become bony with age; it is, however. unclear why this should be the case and at what age this occurs (Benjamin, *et al.* 2002).

The biochemistry of fibrous entheses is also poorly understood. However, by analogy from the periodontal ligament enthesis, this differs from other attachment sites in that it attaches to cementum and not bone (Benjamin, *et al.* 2002). Collagen types I and III, as well as lumican and fibromodulin, have been found. These proteoglycans are lost once the tendon has entered the bone, and this removes the interfibrillar spaces. However, according to Benjamin and colleagues (*ibid.*), this probably does not occur at fibrous entheses other than the periodontal ligament, but why this should be the case is unclear.

The soft tissue attaches directly to bone in adults or indirectly to the periosteum, during the growth period. The collagen fibres of the soft tissue run almost parallel to the long axis of the bone, and approach the enthesis at an oblique angle. Fibrous entheses tend to be broader than fibrocartilaginous ones (Benjamin and Ralphs 1999).

3.3.3.1 Development

Fibrous entheses need to migrate towards the end of the growing bone to maintain the same relative position with respect to the joint upon which they act (Benjamin and Ralphs 1999). For the attachment site to do this, the enthesis is attached to the periosteum during growth (*ibid.*). The metaphyseal position of the medial collateral ligament is maintained by interstitial growth in the periosteum, erosion of the bone at the leading edge of the enthesis and deposition of bone at the trailing edge (*ibid.*). Therefore, the absence of fibrocartilage at metaphyseal insertions is a consequence of development (*ibid.*).

The developmental sequence of attachment growth was studied using immature rabbits (Hurov 1986). Tendon mediated entheses on the diaphysis were found to

attach to the periosteum during all stages of growth examined. The semitendinosus muscle on the femur was found to also attach to a layer of fibrocartilage, hyaline cartilage and chondroid bone (calcified cartilage) at the final stage (60 days). This is similar to the attachment of the rabbit medial collateral ligament at 60 days (see above). In contrast the extensor retinaculum on the tibia was found to attach to the periosteum and course-fibered periosteal bone in the penultimate stage studied (49 days) and to periosteum and lamellar bone in the final stage (again 60 days). In contrast the popliteus muscle attachment on the femur, which is not mediated by a tendon, was attached to the periosteum in all stages studied.

3.4 Beneath the enthesis

Fibrous entheses generally have a thicker area of cortical bone below the enthesis compared to fibrocartilaginous entheses, although this only applies to the appendicular skeleton. The reasons for this are unclear, but Benjamin *et al.* (2002) suggest that nutrient transfer is a probable cause. However, these authors also state that fibrocartilaginous entheses occur at epiphyses and apophyses; perhaps the reason for the thinner cortical bone relates instead to the biomechanical needs, especially in relation to apophyses where stiffer bone might result in injury. It has been proposed that tuberosities are not loaded in impact and therefore do not have a shock-absorbing role; the thin layer of cortical bone transfers the stress to the cancellous bone which in turn transfers it to the compact bone (Currey 2002).

Benjamin *et al.* (1992) found that the ratio of subchondral bone to marrow was not related to force or range of movement, but to functional or developmental factors. However, Benjamin and Ralphs (1998) hypothesized that the thickness of the subchondral plate may change in response to loading even in mature individuals, perhaps in response to movement at the interface between hard and soft tissues (perhaps this is what Benjamin *et al.* (2002) meant by "*functional factors*"). Kumai *et al.* (2002) found that the subchondral plate was absent at the attachment sites of some anterior talo-fibular ligaments. However, they could not be certain whether this was due to disease.

The boundary between calcified fibrocartilage and subchondral bone at a fibrocartilaginous enthesis is very irregular, and has been likened to jigsaw pieces in the way that they interlock; it has been argued that this interlocking is more important than the collagen fibres that cross into the bone (Benjamin, *et al.* 2002; Milz, *et al.* 2002). This is because this portion of the enthesis is continuously eroded and remodelled during development (see Sections 3.3.2.1 and 3.3.3.1) (Benjamin *et al.* 2002). It is possible that this means that the collagen fibres themselves are not always continuous from tendon through to bone, or that they are not always surrounded by the bone matrix and therefore not anchored in. However, Clark and Stechschulte (1998) found that collagen fibres were continuous up to the point where they terminated in the patella and they "*sometimes turn and splay as they interdigitate with bone*" (ibid. p. 614), perhaps indicating that they do have an anchoring role. Hems and Tillmann (2000) found that the collagen fibres did not cross intact osteons and could be detected in "*the region of the intermediate lamellae only*" (ibid. p. 202), but it is unclear exactly what this phrase means with regard to the terminology used in this chapter.

Although the calcified fibrocartilage/bone junction is highly irregular, the soft tissues actually fall away at the "tidemark", which is the smooth junction between unmineralised and mineralised fibrocartilage (see Figure 3.1). Consequently, a healthy fibrocartilaginous enthesis should leave a smooth, well-defined mark, devoid of vascular foramina on the skeletal surface (Benjamin *et al.* 2002). Periosteal fibrous entheses also leave smooth markings on the bone surface. However, these are less clearly defined and cover a larger surface area than fibrocartilaginous entheses.

Fibrous entheses, on the other hand, are anchored by their collagen fibres. Deposition of bone matrix around the fibres during the developmental process creates a layer of bone that is formed of ossified tendon (Benjamin *et al.* 2002). This bone is highly cellular and crossed by fibres, but it is unclear whether these are collagen fibres or ossified forms of them (Beresford 1981; Hems and Tillmann 2000). There are broad lacunae and young osteocytes (Beresford 1981) and there is no lamellar structure (Hems and Tillmann 2000). This type of bone has been given many different names; *Einstrahlungsknochen*, ß chondroid bone (Beresford 1981), fiber bone (Hems and

Tillmann 2000) and bundle bone (Benjamin *et al.* 2002; François *et al.* 2001). Consequently, bony fibrous entheses leave roughened or raised markings on the skeletal surface (Benjamin *et al.* 2002). It is unclear, however, how rough and how raised these ridges should "normally" be and whether these can change depending on workload, injury or age. According to François *et al.* (2001), lamellar bone slowly replaces bundle bone; this might affect the appearance of these surfaces, but it is unclear what time frame is involved.

Trabeculae orientation in bone generally reflects the principal direction of strain (Benjamin *et al.* 2002) and this hypothesis appears to cover entheses as well. It has been found (Biewener, *et al.* 1996) that trabeculae in the poteroo calcaneus align to the compressive/tensile strain axis in the overlying cortical bone. The alignment itself occurs before skeletal maturity. Once aligned, the structure is thought not to change orientation, although the authors do not know if changes in the principal strain axis due to exercise might have an effect (Biewener, *et al.* 1996). Other authors have demonstrated that the trabeculae appear to continue the alignment of tendon collagen fibres from the Achilles tendon to the plantar fascia, thereby transmitting load from one to the other (Milz, *et al.* 2002). Finite element stress analysis of trabeculae architecture below entheses might be able to provide further insight into loading patterns in skeletal material, once the role of exercise in their remodelling is understood.

3.5 Abnormalities at Entheses

In this section all abnormalities, whether destructive or proliferative, are called enthesopathies (Erdem, *et al.* 2005). They are divided into two sections: one on the formation of bone spurs and the other on destructive lesions at entheses.

3.5.1 Bone Spur Formation

Bone spurs occur in a number of diseases, most notably ankylosing spondylitis and diffuse idiopathic skeletal hyperostosis (Benjamin *et al.* 2002), but they are also found as a response to injury (Benjamin, *et al.* 2002; Benjamin and Ralphs 1996; Rufai 1995), and some authors also suggest that their presence increases with age (Benjamin, *et al.* 2000; Moriggl, *et al.* 2001; Rufai 1995). In this section, the composition and origin of spurs will be discussed. Causes of spur formation will be discussed in Chapters 4 and 5.

In a study of the human Achilles tendon structure and pathology, 16 out of 50 cadavers studied had a bone spur at the Achilles tendon insertion (Rufai 1995). These bony growths extended from the calcaneus into the tendon and were most commonly found in the postero-inferior portion of the enthesis. Traces of calcified fibrocartilage from the original enthesis could be detected within the spur, and the tidemark of the enthesis itself was highly irregular. Extracellular matrix surrounded these spurs (*ibid.* p. 591). More recently, Moriggl *et al.* (2001) found that this extracellular matrix was rich in type II collagen and aggrecan, suggesting that the type of ossification that creates these spurs is endochondral in character. Perhaps the aggrecan found indicates a high level of compression at the enthesis during spur formation.

These spurs are found in a number of conditions, *e.g.* tennis elbow, and jumper's knee (Benjamin, *et al.* 2002; Benjamin and Ralphs 1996). These injuries probably stem from repeated strain, which causes formation of new fibrocartilage and this eventually becomes bone (Rufai 1995). This explains the presence of fibrocartilage in and around the spur itself, as described above (Abreu, *et al.* 2003; Rufai 1995). The long-term effects of loading on the enthesis are probably the cause of the increased frequency of spurs in the elderly.

It has been proposed (Niepel and Sitaj 1979) that bone spurs develop as a response to micro-tears at an enthesis. According to these authors, this leads to the proliferation of fibroblasts and the appearance of granulomatous tissue, followed by ossification. Other authors suggested that they are buttresses, which either act as stabilisers for

micro-cracks or reduce the damage of wear and tear (Gibbon and Long 1999; Kumai and Benjamin 2002).

It has been found that there is a correlation between the presence of osteophytes and enthesopathies, leading authors to suggest that some people are natural "bone formers" (Rogers, *et al.* 1997). Moriggl *et al.* (2001, p. 544) hypothesised that the mechanical stimulus triggers interactions between genetically controlled proteins, activins and possibly transforming growth factors; it is possible that the genetically controlled proteins are the cause of this correlation, as the same proteins are also likely to control bone remodelling at joints.

It seems clear that fibrous entheses do not form spurs, a fact that has not been taken into account when using these spurs as indicators of mechanical stresses in archaeological populations. This is perhaps best seen in the papers that score these lesions in terms of severity, from ridges and crests at the enthesis, via patches of destruction to bone spur formation (Hawkey 1998; Hawkey and Merbs 1995). It is, instead, probable, that the ridges and crests are just the normal appearance of fibrous entheses but, having said, that both papers (Hawkey 1998; Hawkey and Merbs 1995) depict spurs on the diaphysis of the humerus, an area that, in theory, should only have fibrous attachments. The question that needs to be answered in these cases is whether these exostoses are related to entheses or have another origin.

The biochemistry of spur formation and other ectopic soft tissue mineralization has recently been studied (Yoshizawa, *et al.* 2004). These authors found that Runx2/Osf2 transcriptional activity was repressed by Msx2 in conjunction with TLE1 and that HDAC is required for this to work. Runx2/Osf2 is involved in osteoblast differentiation and bone formation. Msx2 is thought, by the authors, to have two effects: in bone it inhibits osteoblasts differentiation while promoting osteoprogenitor proliferation during bone development, and it inhibits mineralization of the extracellular matrix. The authors also demonstrated that Msx2 has to be down-regulated if extracellular matrix is to be mineralized, and that this seems to occur in the mineralized regions in OPLL (ossification of the posterior longitudinal ligament). Therefore, factors which down-regulate Msx2 are candidates for OPLL risk factors. Genetic backgrounds have been analysed, but the contribution of this to other factors,

including age and sex, is poorly understood. Whether similar mechanisms are involved in other ossifying diseases, or bone spur formation caused by physical stress, is not known.

3.5.2 Destruction of the Enthesis

Longitudinal fissuring can often be seen in fibrocartilaginous entheses. This is very similar to the fissuring observed in early stage osteoarthritis. In entheses, clusters of large rounded cells form at the margins of the enthesis and they become filled with an "*amorphous metachromatic material*" (Benjamin and Ralphs 1997, p. 1141) or with a disorganised fibrous extracellular matrix *(ibid.)*; this probably represents an attempt at healing the fissure (Benjamin and Ralphs 1999). Radiographs often demonstrate calcification in these regions.

Transverse fissures can also develop, but these are normally smaller than the longitudinal ones and are filled with a loose connective tissue that is vascular (Benjamin and Ralphs 1997). These occur most frequently at the junction of the unmineralised and mineralised zones (Benjamin and Ralphs 1999). Cell response has not been documented (*ibid.*).

3.6 Chapter summary

Two types of enthesis are found on long bones: these are fibrocartilaginous and fibrous. These can be recognised on skeletal remains by the marks that these entheses leave on bone. The normal skeletal appearance has a significant impact on the recording of MSM, as roughness must be interpreted differently at the different sites. This will be discussed further in Chapter 6.

The formation of bone spurs depends on their location, but they seem to be formed by endochondral ossification. Many factors are involved in their formation, and these

will be discussed in Chapters 4 and 5. Biochemical work has been performed recently, which provides insights into the underlying mechanism and cause of spur formation. Further research in this field is required to understand how mechanical stress affects the biochemistry of this region. This would enable the underlying causes to be understood better, and might enable chemical tests on spurs to determine whether a disease process or mechanical stress has caused their formation. Unfortunately, destruction at entheses is less well understood; further research in this area to determine processes of lesion formation and their relationship to mechanical stress is needed.

Chapter 4. Factors Affecting Attachment Sites: Physical Stress

4.1 Introduction

This chapter considers the traumatic incidents (physical stress) that can cause changes to attachment sites and the healing processes which cause these injuries to be seen in skeletal remains. Soft tissue healing has also been considered because this often has a long-term effect on the functionality of the enthesis and joint. Traumatic changes to articular cartilage are also considered, as this is very similar in character to enthesis fibrocartilage. For this reason it is thought that parallels can be drawn to increase the, otherwise limited, studies on enthesis trauma.

4.2 Healing of soft tissue and entheses

Soft tissue healing has been included in this review because of the role it has in distributing physical stress to the bone. In addition, soft tissues occur in close proximity to entheses and bone, and injuries to these can affect the bone itself. An extreme example of this is limb atrophy following muscular paralysis (examples in Aufderheide and Rodríguez-Martín 1998, p. 212 and (Birkett 1986), p. 298). However, in less extreme cases, soft tissue injuries can cause avulsion injuries. Skeletal disuse (as might occur after tendon rupture) can cause resorption of bone at entheses (Benjamin, *et al.* 2002). Another reason for including tendons and ligaments, as well as bone, is that injuries often occur at either side of an enthesis, *i.e.* in the bone or soft tissue, but not across the junction between the two (Kumai, *et al.* 2002).

4.2.1 Soft tissue

Tendon healing, and it is not clear (Mukherjee, *et al.* 1996) whether this also applies to ligament and fascia, can be divided into four key stages: inflammation, repair, remodelling, and maturation (Table 4.1). Prior to the inflammatory stage, blood is released into the wound (normally a gap in the tendon); this clots and the fibrin in the clot stimulates a histamine reaction that stimulates blood flow (Andriacchi, *et al.* 1988). Other vasodilators are also released, increasing cell permeability and allowing inflammatory cells (erythrocytes, leukocytes, and lymphocytes) into the wound. The inflammatory process is initiated by intrinsic (epitenon and endotenon) and extrinsic (paratenon) tissues (Gelberman, *et al.* 1988). During the inflammatory stage, granulation tissue is formed (Mukherjee, *et al.* 1996). The granulation tissue and inflammatory cell presence overwhelms the tenocytes. Cells in the granulation tissue have phagocytic properties and are probably involved in "mopping-up" debris and necrotic tissue (Andriacchi, *et al.* 1988; Gelberman, *et al.* 1988). The inflammatory stage is also characterised by swelling, caused by the increased water content of the tissue (Andriacchi, *et al.* 1988). This stage probably maintains the formation of new blood vessels required for healing, but it is influenced by factors such as age, genes and disease (Hart, *et al.* 1995). Although, inflammation is an important stage in tendon healing, in cases of repetitive injury in which inflammation has become chronic, it may have the opposite effect (*ibid.*). During the inflammatory phase the tendon is severely weakened because the tendon is only held together by blood clots (Gelberman, *et al.* 1988). Consequently, recurrent inflammation will result in prolonged periods of tendon weakness.

Table 4.1 Stages of tendon healing ((Andriacchi, *et al.* 1988; Gelberman, *et al.* 1988; Lin, *et al.* 2004; Mukherjee, *et al.* 1996; Weintraub 2003).

Stage	Sub-stages	Characteristic	Comment
Inflammation	Prior to inflammation	Blood released into wound. Blood clots.	
	Inflammatory stage I	Blood clot stimulates release of vasodilators, platelets and pro-inflammatory cells	Factors causing inflammation may come from extrinsic, intrinsic or a combination of both sources. This may be dependent on location of wound.
	Inflammatory stage II	Breakdown of necrotic tissue and debris in wound. Recruitment of fibroblasts and angiogenesis leading to capillary growth in wound. Increase of: DNA, fibronectin, glycosaminoglycan, water, and collagen type III, which stabilise the newly formed matrix.	
Repair		Predominantly fibroblasts, with macrophages and mast cells. Collagen type II reaches peak quantity	
Remodelling		Scar becomes translucent and there is linkage between the broken parts. Matrix synthesis by fibroblasts has decreased and collagen fibres being to orient themselves along the long axis of the tendon	
Maturation		Collagen type III is replaced by collagen type I and there is a return towards normal extracellular matrix component ratios.	Maturation can take a year and tendon may never return to normal strength.

The reparative process, after the inflammatory stage is characterised by the production of matrix components which produce a fibrous scar. This matrix changes as the scar is remodelled, and finally during maturation, the scar develops cross-linking at the molecular and interfibrillar levels (Martin 2000). The matrix components, *e.g.* collagen fibres, are produced by fibroblasts infiltrating from surrounding soft tissues (Gelberman, *et al.* 1988; Resnick and Niwayama 1995a). The production of collagen occurs early in the healing phase, for example in the flexor tendons of the hand, and approximately one week after injury (Gelberman *et al.* 1988). Gelberman *et al.* (1988) studied the flexor tendons of the hand. It was found that the fibroblasts which synthesise collagen became the predominant cell type and produced matrix. This is not oriented along the long axis of the tendon, unlike the normal collagen fibres, the collagen is also type I, and not the mixture of types found in a normal tendon. After three weeks, in the flexor tendons of the hand, the endotendon produces fibroblasts, which have the effect of synthesising and resorbing collagen. The effect of this is to remodel the scar, so that the collagen aligns itself with the collagen in the rest of the tendon. This alignment can only occur if the tendon is loaded, rather than immobilised (Amiel, *et al.* 1995). Once the scar has been fully remodelled the fibroblasts revert to tenocytes. Full maturation was found to have occurred one hundred and twelve days post- injury (Gelberman *et al.* 1988).

Biochemical activity in tendons in the region adjacent to the insertion point has been found to change during the healing phase of tendon (Thomopoulos, *et al.* 2002). Thomopoulos *et* al. (2002) studied the gene expression of the extracellular matrix in healing tendon insertion sites to assess this chemical change. Rat *supraspinatus* tendons were detached and repaired using a technique that provides close apposition between the two halves. The chemical changes that occurred 1, 2, 4, 8 and 16 weeks after injury were quantified. Normal rat *supraspinatus* tendons and their insertions were also studied to compare the chemical balance. This histological analysis demonstrated that a week after injury the tendon was hypercellular, and was filled with disorganised tissue. There was no change after four weeks. In the eighth week the tendon appeared less cellular and more organised, and remodelling and reorganisation continued. This led to a decrease in cellularity and an increase in organisation by the sixteenth week. At this time vascularity remained higher than

normal and the tendon retained an abnormal appearance. It should be noted that, despite the discussion of an inflammatory response above (Hart, *et al.* 1995; Mukherjee, *et al.* 1996), no evidence of inflammation or necrosis was found at any stage in this study (Thomopoulos, *et al.* 2002). In the molecular study both collagens and proteoglycans were found in different ratios compared to the normal samples. Collagen type XII, a molecule that acts as a bridge between fibrils and extracellular matrix, was only detected during the healing process, as were the proteoglycans aggrecan and biglycan. Biglycan is thought to increase collagen type I's fibrillogenesis (*i.e.* its ability to form fibrils) (*ibid.*), whereas aggrecan is a large molecule with the ability to hold relatively large amounts of water, thereby contributing to the ability of the tissue to withstand compression (*ibid.*). Gene expression of collagen type I was increased during the entire healing process. This was expected because this is the primary component of tendon. The only molecule to decrease in expression was decorin. Although little seems to be known about the function of decorin, it is thought (*ibid.*) that it might inhibit type I collagen fibrillogenesis. It was found that all molecules which increased in expression slowly decreased in expression during the time period studied (eight weeks). However, they remained at higher than normal levels. Proteoglycan levels also remained higher than normal even after full maturation of the scar (Andriacchi, *et al.* 1988).

Ligament healing is also characterised by these stages (Resnick and Niwayama 1995a). However, both structures require close apposition of the ends of the lesion, and consequently complete ruptures of either structure do not always completely heal (*ibid.*). One other important factor in tendon and ligament healing is the positive effect of motion on healing (*ibid.*). It is possible that this stimulates cell activity in these structures, thus speeding up the healing process.

Four stages of ligament healing have been defined (Andriacchi, *et al.* 1988): Phase 1 involves oedema, hypercellularity and matrix synthesis. Phase 2 continues the matrix synthesis and cell proliferation also occurs. It is during this phase that collagen turnover peaks. In Phase 3 the collagen components return to normal and Phase 4 is characterised by further maturation. This final phase takes months or even years. However, it should be noted that Andriacchi *et al.* (1998) point out that inferring

human healing patterns from animal models, like the one used to characterise these healing phases, can be misleading; particularly when it comes to the time scales involved. They also point out (as did Hart *et al.* 1995) that systemic factors, age, and factors local to the injury site affect the healing process.

The case studies discussed above demonstrate that, not only is knowledge of tendon and ligament healing incomplete, but also that tendons and ligaments never return to their previous state at sites of injury. It is possible that the changes in material properties occurring after a traumatic incident to one of these soft tissues affects stress dissipation and loading characteristics of the tendon or ligament (Lin, *et al.* 2004). These changes might affect the whole system, including the enthesis, thus contributing to MSM formation. However, it should be noted that this is only a possibility. Finite element analysis of the stresses in the system pre- and post-injury would probably be the best method of testing this hypothesis. It should also be noted that studies of herbal remedies indicate that they can have an effect on ligament repair (Fung and Ng 2005). Others indicate that the inflammatory response can be changed by down regulating mast cell activation (Kim, *et al.* 2003). It is possible that other traditional herbal remedies had similar effects and this should be considered in palaeopathological research.

4.2.2 Entheses

The tendon insertion studied by Thomopoulos *et al.* (2002) was that of the rat *supraspinatus* enthesis on the humerus. This enthesis, as stated above, is fibrocartilaginous. Microscopic examination of the site one week after injury revealed that there was a massive cellular response at the enthesis, but no fibrocartilaginous zones, and with no collagen fibres crossing into the bone. After four weeks, there was still no evidence of fibrocartilage at the enthesis, but the tendon itself was beginning to integrate with the bone. At eight weeks all specimens showed some integration of tendon and bone, while only some showed evidence of fibrocartilage at the interface. It is not clear from the article (*ibid.*), whether all specimens had a zone of fibrocartilage after sixteen weeks (this was the end of the experiment). This lack of

fibrocartilage in many of the specimens is probably related to the presence of decorin at the insertion site. Decorin is not normally found at fibrocartilaginous entheses, but is found in a normal tendon. Therefore, according to the authors (*ibid.*), the insertion site is tendinous in character rather than fibrocartilaginous, whilst decorin is present. This indicates that cells at the insertion site were not producing fibrocartilaginous matrix. The decrease in collagen type X expression is also indicative, according to the authors (*ibid.*), of the poor healing ability of the insertion site. It has been hypothesised (*ibid.*) that collagen type X defines the transition of the tissue from cartilage to bone, and it is its structural properties (*i.e.* the hexagonal shape of the molecule) that enable efficient load transfer between these two very different tissues.

Protoglycans are prevalent at entheses, and there are a number of different forms (, each with different functions (Thomopoulos, *et al.* 2002). It has been found (*ibid.*) that the proportions of these molecules change in response to injury and over the period in which the enthesis heals, at least in the case of rats. These authors also found that the proportions of other molecules, notably the collagens (collagen types I, X, and XII) and alkaline phosphatase, also changed with, and during, the period of healing. Collagen type XII was only detected during healing and not in the normal enthesis (but it is possible that it was missed because normal levels might be extremely low, according to the authors). There was elevation of collagen type I and alkaline phosphatase levels throughout the healing phase. On the other hand, collagen type X levels were decreased throughout the healing phase. Type XII collagen is thought to function as a bridging molecule between fibrils and other components of the extracellular matrix (*ibid.*). This molecule is particularly associated with type I collagen, which forms fibrils and is, for this reason, one of the most important components of the soft tissue portion of the enthesis and the tendon itself. It is, in fact, these fibrils that are the primary building blocks of the tendon; consequently, it is these that need immediate repair after injury to retain structural integrity. The cause of the decrease in collagen type X is unclear, mainly because it is not yet fully known what the role of this molecule is (*ibid.*). According to Thomopoulos *et al.* (*ibid.*), the decrease might be the cause of poor healing in tendon injuries. This is an important point, as tendon injuries often heal badly and the cause could be this change in levels of collagen type X.

4.2.3 Bone

Remodelling of bone also occurs in response to normal loading and overloading. It is probable that overuse injuries and injuries causing avulsions of fragments of bone are concurrent with an overloading episode. Consequently, understanding the response of bone to this event is also important when discussing injuries to entheses.

Normal loading of bone has been found to produce biochemical changes in the matrix that persist for at least twenty-four hours; at least this is the case in avian and canine bone (Lanyon 1987). Proteoglycans, found in proximity to the cells of bone (as well as in other structures, notably entheses, according to Thomopoulos *et al.* 2002), changes their orientation and this change might be the stimulus required to remodel bone (Lanyon 1987). However, this might not be the only factor in remodelling, according to Lanyon (*ibid.*); other possible factors include change in cell shape caused by strain, fluid flow changes around the cell caused by strain, and electrical current changes caused by charged fluid flow. It should be noted that it is not clear from Lanyon (*ibid.*) whether overload stresses increase the effect of these changes nor, if there is an increase, whether this is proportional to the increase in stress.

Injury to bone can have dramatic effects, *e.g.* fracture or avulsion. However, microfractures or microcracks are probably the most common forms of injury. Microcracks in bone can be repaired in two ways (Boyde 2003). Firstly, they can be repaired by calcified tissue remodelling. This process increases osteoclastic activity, thereby removing bone; followed by increased osteoblast activity which fills in the crack and the area of bone removed by the osteoclasts. The second method of repairing microcracks also occurs in calcified articular cartilage and this involves the infilling of the microcracks with calcified matrix. Although this latter mechanism is not well understood, it is probable according to Boyde (*ibid.*) that the extent to which this occurs is underestimated because of the continued remodelling of bone. Palaeopathologically these types of injuries could only be detected using microscopy.

The healing response of bone, *i.e.* infilling of microcracks and remodelling, which is probably stimulated by biochemical changes caused by physical stress (Boyde 2003; Lanyon 1987), has been described, as has the healing response of the soft tissue portions of an enthesis. However, it is unclear how the calcified portions (*e.g.* mineralised fibrocartilage and subchondral bone) are affected during this process. Unfortunately, it is primarily these zones that are of interest to osteologists studying MSM formation.

4.3 Physical stress

This section provides a brief introduction to physical stress, its causes (particularly occupation-related causes), and the effect on the entheses of the skeleton. Physical stress is defined here as any stress or strain of the musculoskeletal system. Musculoskeletal disorders refer to conditions that involve the nerves, tendons, muscles and other supporting structures of the body (*e.g.* the skeleton) (Putz-Anderson, *et al.* 1997). Often these arise in relation to repetitive tasks occurring in the work place, and it is these that will be the primary concern of this section.

Occupational related health disorders have been recognised since the Renaissance. The first doctor to advocate that physicians should determine their patient's occupation was Bernadino Ramazzini (1633-1714) (Bamford 1995). Other doctors have noted the use of occupational markers to identify the dead or amnesic. One such doctor was Dr. Ronchese (Ronchese 1948), who described skin changes that could be related to a specific occupation or hobby, as well as skin changes that were pseudo-occupational. There is one exception in his list of lesions, that of a dancer or gymnast able to perform the "splits"; this exception notes the 'peculiar divaricability of the legs' (Ronchese 1948, p. 35) and the 'hypertrophy of the muscles of the calves' (*ibid.*), but noted that these features may also be present in Ehlers-Danlos syndrome as an exaggerated laxity of the joints. It is these types of changes caused by physical stress that are useful for bioarchaeologists. However, as can be seen in this example, these changes cannot always be solely attributed to one cause and many, as will be seen below, are of multifactorial origin.

4.3.1 Physical Stress: Work-Related Factors

In the industrialised world, according to the World Health Organisation (Luttmann, *et al.* 2003; Putz-Anderson, *et al.* 1997), one third of health-related absences from work are caused by musculoskeletal disorders. Of these, back injuries are the most common, followed by upper limb and neck injuries, and injuries to the knees and hips. These disorders are generally thought to be triggered or exacerbated by workload or work-related physical stress.

There have been a variety of terms used to describe those upper-extremity musculoskeletal disorders thought to be related to repetitive trauma: repetitive strain injury (RSI), occupational overuse syndrome (OOS), occupational cervicobrachial disorder (OCD), and cumulative trauma disorder (CTD) (Sluiter, *et al.* 2001). The term "work-related upper-extremity musculoskeletal disorders" is the preferred terminology of many authors because it is thought to reflect the multifactorial aetiology of these disorders (*ibid.*). The WHO definition of multifactorial, in this context, is that the work environment, and performance of work, contribute to the disorder along with many other factors (*e.g.* age, and sex) (Sluiter, *et al.* 2001). Lifestyle factors, such as smoking and obesity (Putz-Anderson, *et al.* 1997), but also non-work activities, such as sport and hobbies, also play a part.

In the case of upper extremity musculoskeletal disorders it has been found that there is more direct evidence for the effects of physical work factors on their development than for the effects of non-physical factors in the workplace (Sluiter, *et al.* 2001) (*e.g.* psychological, which is considered important in clinical settings, *ibid.* Sluiter *et al.* 2001). The physical factors include: extreme posture, movement, force and vibration (*ibid.*) elevated body mass index, history of or current carpal tunnel syndrome, history of past or current back pain, grip type, and wrist motion (Putz-Anderson, *et al.* 1997). Risk factors for back disorders (and some shoulder disorders) include heavy physical work, lifting and forceful movements, bending and twisting, whole body vibration, and static work postures *(ibid.)*. It is the duration and/or frequency of these factors which also determine the occurrence of these disorders. The duration of the activity is

defined by the WHO (Luttmann, *et al.* 2003) as the number of repetitions per unit time, and the total exposure time (*e.g.* months or years). Disorders associated with short-term exposure are normally acute, whereas those associated with long-term exposure are often chronic.

Although there have been many studies of work-related upper extremity musculoskeletal disorders, there is still considerable controversy and uncertainty regarding the aetiology of these disorders, according to Sluiter *et al.* (2001). The primary problem is the difficulty of assessing the validity of epidemiological research caused by, among other things, the use of different definitions and diagnostic criteria for these conditions (*ibid.*). Determining exposure levels is also considerably difficult (*ibid.*). However, a recent literature review (Putz-Anderson *et al.* 1997) of epidemiological studies of work-related upper extremity (and back) disorders found the following (see Table 4.2). There was insufficient evidence (defined as studies of insufficient number, quality, consistency or statistical power, *ibid. p. xii)* to determine the presence of a causal link for: force, vibration and shoulder disorders; repetition and posture and elbow disorders; posture and carpal tunnel syndrome; static work posture and disorders of the back. There is evidence, according to Putz-Anderson *et al.* (1997), that there is a causal link between repetition and shoulder disorders, carpal tunnel syndrome and tendinitis; posture and shoulder and back disorders, as well as tendinitis; force and elbow disorders, carpal tunnel syndrome and tendinitis, vibration and carpal tunnel syndrome; and heavy physical work and back disorders. Finally, there is strong evidence, according to Putz-Anderson *et al.* (1997: xii), for: a combination of different factors and most of the disorders studied (elbow disorders, carpal tunnel syndrome, and tendinitis, but not shoulder disorders), while both hand and arm vibration syndrome and back disorders were strongly linked to vibration. The strong causal link between combinations of factors and individual disorders and syndromes again highlights the multi-factorial origin of work-related musculoskeletal disorders. However, there is still limited quantitative detail regarding the relationship between the disorder and exposure to these factors (Putz-Anderson *et al.* 1997).

Table 4.2 Causal links between activity and upper limb musculoskeletal disorders adapted from Table 1 in (Putz-Anderson *et al.* 1997, p. xii).

Strength of evidence	Activity	Disorder
Insufficient evidence	Vibration	Shoulder disorders
	Force	Shoulder disorders
	Repetition	Elbow disorders
	Posture	Elbow disorders
	Posture	Carpal tunnel syndrome
Evidence	Posture	Shoulder disorders
	Repetition	Shoulder disorders
	Force	Elbow disorders
	Repetition	Carpal tunnel syndrome
	Force	Carpal tunnel syndrome
	Vibration	Carpal tunnel syndrome
	Repetition	Tendinitis
	Force	Tendinitis
	Posture	Tendinitis
	Awkward posture	Back disorders
	Heavy physical work	Back disorders
Strong evidence	Combination of posture, repetition and force	Elbow disorders
	Combination of posture, repetition, vibration and force	Carpal tunnel syndrome
	Combination of posture, repetition and force	Tendinitis
	Vibration	Hand and arm vibration syndrome
	Lifting with a forceful movement	Back disorders
	Whole body vibration	Back disorders

According to the WHO guidelines (Karjalainen 1999) for statistical classification of diseases, it is difficult to link musculoskeletal diseases to work, as they are often multifactorial. However, the WHO has guidelines for recording these diseases, their cause and the occupations most likely to be involved in these changes. These are shown in Table 4.3. Further examples of occupations predisposing to musculoskeletal injury are: health workers, farmers, veterinarians (all back pain), production line workers (back pain, upper limb disorders and other musculoskeletal disorders), shelf fillers (back pain and other), supermarket cashiers (back pain, upper limb and other musculoskeletal disorders), food preparation workers (back pain, upper limb and other musculoskeletal disorders) (Foster 1995).

Table 4.3 List of diseases/disorders, their causes and the occupation/industry with which they have been associated, adapted from (Karjalainen 1999, p. 29).

Code	Disease	Agent	Occupation/Industry
M65.-	Synovitis and tenosynovitis M65.4 Radial styloid tenosynovitis (de Quervain)	Repetitive movements, forceful exertions and extreme postures of the wrist. Especially a combination of these risk factors	Work involving repetitive movements, forceful exertions and extreme postures of the wrist, e.g. meat, fish and poultry processing, construction and carpentry, electronics assembly, textile work
M70.-	Soft tissue disorders related to use, overuse and pressure		Same as above
	M70.0 Chronic crepitant tenosynovitis of hand and wrist	Repetitive movements, forceful exertions and extreme postures of the wrist. Especially a combination of these risk factors.	Same as above
	M70.2 Olecranon bursitis	Prolonged pressure of the elbow region	
	M70.4 Prepatellar bursitis	Prolonged stay in kneeling position	Carpet and floor layers
M77.-	Other enthesopathies M77.0 Medial epicondylitis M77.1 Lateral epicondylitis	Repetitive forceful work	Construction workers, such as wallboard installators, roofers and masons, meat cutters, packers, other work involving repetitive and forceful movements

4.3.2 Mediating factors (non-work-related factors)

These mediating factors include extrinsic and intrinsic factors. Examples of extrinsic factors include the working temperature (low working temperature is associated with a decrease in dexterity), and whether an individual is involved with sporting or domestic activities. Intrinsic factors are those that cannot be altered by an individual, such as age and sex. This section will briefly address some of these factors and their effect on musculoskeletal disorders.

Age-related factors include the degenerative processes that develop over time, including tissue strength loss and the increase in number of years in a particular job (Putz-Anderson, *et al.* 1997). However, it has also been discovered that individuals who undertake a task or job and who rapidly develop symptoms, often leave their job, thus leaving only those who are less prone in the work-force (*ibid.*). Sex differences have been difficult to study epidemiologically because males and females are often employed in different types of roles (for example, females are often employed in hand-intensive roles), thereby making true comparisons based on sex, impossible (*ibid.*). The relationships between smoking and back disorders have not been fully explained (*ibid.*). Hypotheses proposed are: increased coughing casing stress on the abdominal muscles, diminished blood-flow in vulnerable tissues, diminished bone-mineral content leading to microfractures (*ibid.* p. B-4).

Physical activity is a more complicated subject. While physical activity may cause injury, no physical activity increases the risk of injury, and once an injury has occurred the threshold limit for further injury is reduced (Putz-Anderson, *et al.* 1997). It is generally accepted that physical activity is a way to reduce the risk of work-related musculoskeletal disorders; epidemiological studies do not reinforce this simple relationship (*ibid.*). On the other hand, epidemiological studies in sports medicine do tend to support this view, at least in those activities which involve forceful repetitive movements, *e.g.* tennis (*ibid.*). This is despite the longer recovery periods which professional sportspersons enjoy, compared to the average manual worker (*ibid.*). Perhaps this reflects the fact that pushing the body beyond a threshold limit of force and repetition reduces the body's ability to recover even if the recovery time is longer.

For this reason it is possible that data from sports medicine cannot be used as a model for normal and work-related activity in anything except unusual circumstances.

Strength has not been fully studied epidemiologically and it was found by Putz-Anderson *et al.* (*ibid.*) that no conclusions could be fully drawn from the reports that do exist. In the case of anthropometric data, drawing conclusions from the data that exist was again difficult. However, it was found by these authors in their review that obesity is a risk factor for developing carpal tunnel syndrome, possibly because of the increased fatty deposits or because of increased hydrostatic pressure in the obese (*ibid.*).

4.3.3 Bone Spur Formation: causes in the upper limb

Enthesopathy is defined as any abnormal change to an enthesis, so includes bone spurs and destructive lesions. This section is divided into upper and lower limb changes. The upper limb is the primary focus of this thesis because of its close association with occupationally related diseases, as can be seen from the clinical literature discussed in the previous sections. However, there is so little written on bone changes that the literature had to be supplemented with research on the lower limb. It has had to be assumed that lower limb changes can be applied to the upper limb. This will be discussed in Section 4.3.4.

This section covers enthesopathies in the upper limb and their associated pathologies, *e.g.* rotator cuff disease and impingement syndrome, and their relationship to physical stress. Most cases discussed are from the clinical literature. However, there are two cases from the palaeopathological literature which are relevant to the discussion. These are discussed where appropriate.

Researchers (*e.g.* Lee and Lang 2000) often link impingement syndrome to rotator cuff disease. It is unclear whether they are in fact two separate conditions or just different clinicians' definitions of the same process. Lee and Lang (2000, p.126) define impingement syndrome as the '*painful entrapment of the supraspinatus tendon.*

subacromial-subdeltoid bursa, and biceps tendon between the humeral head and the coracoacromial arch'. Three stages of impingement have been defined. Stage 1 usually affects patients under the age of 25, and is seen as oedema and haemorrhage, both of which are reversible (Lee and Lang 2000). Stage 2 most frequently affects patients between the ages of 25 and 40, and the characteristic signs of this stage are fibrosis and tendonitis of the rotator cuff (*ibid.*). The final stage, normally affects individuals over the age of 40, and is characterised by degeneration and rupture of the *supraspinatus* tendon, with associated subacromial bone spurs (Lee and Lang 2000). These spurs are probably caused by traction associated with repeated impingement of the greater tuberosity on the coraco-acromial ligament (Resnick and Niwayama 1995a). As can be seen from this, age-related phenomena seem to be significant for spur formation.

However, some researchers (Ogata and Uhthoff 1990) found that enthesopathies on the inferior aspect of the acromion were not correlated with aging. These spurs were found to be formed by endochondral ossification, and lined up with the fibres of the coraco-acromial ligament. A fibrocartilaginous layer on the inferior aspect had to be present for the formation of these spurs, according to the authors, but it was unclear whether this was a causative factor in impingement syndrome, or a response to pressure within the sub-acromial compartment (*ibid.*). Tensile forces were proposed by the authors as the cause of the spurs themselves, but it was unclear from the article why they thought this.

Sub-acromial spurs have also been described in the palaeopathological literature. Miles (1998) described two cases from the $18^{th}/19^{th}$ century AD site of Christ Church, Spitalfields, London (a known age skeletal sample). These spurs were found on the anterior surface of the acromion and continued in the direction of the coraco-acromial ligament (which was still present in the form of mummified tissue). The spurs were situated between the tip and medial margin of the acromion in both individuals (Miles 1998), and this is characteristic of enthesopathy formation in impingement syndrome, (Resnick and Niwayama 1995a). The individuals studied were female and over the age of sixty and, although it is possible that age may have been a factor in the

enthesopathy formation, it cannot be known from skeletal samples at what age the bone formation originally occurred.

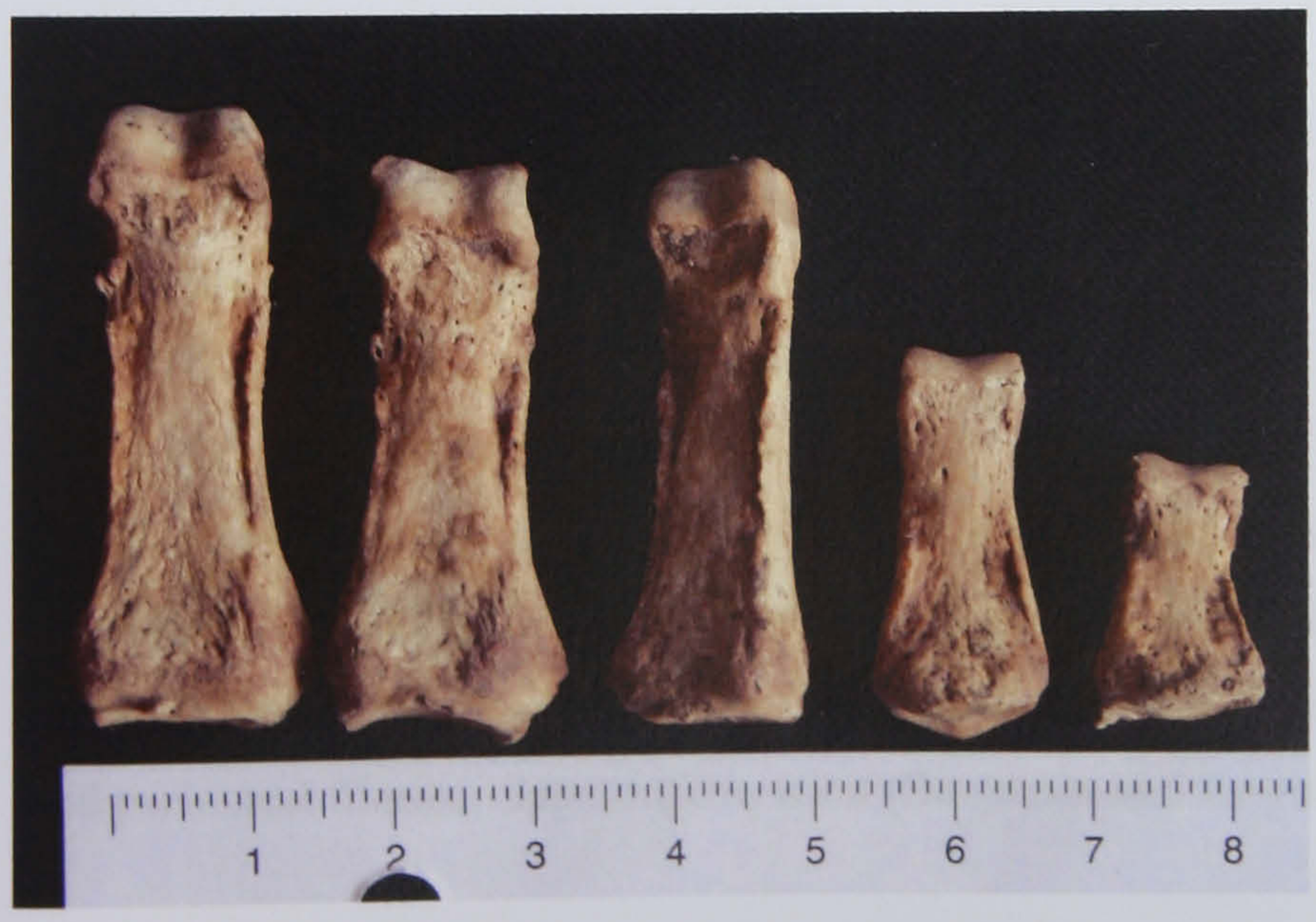
Authors (Rasing and van Kampen 2000) have also defined enthesopathies as the prominence of an enthesis. In the case described by Rasing and van Kampen (*ibid.*). this could be directly associated with long-term musculoskeletal stress. In a fifty-year-old male mechanic an enthesopathy formed at the enthesis of the biceps on the right radius. Initially, pain was only present during hard labour, but the pain became progressively worse, and after a time he also experienced pain in the left elbow. There was no history of trauma or disease and the individual was right-handed. Radiographs of the right and left elbow showed signs of prominent radial bicipital tuberosities (the attachment of the *biceps brachii*) and thickened bursae. It was these prominences that the author defined as enthesopathies (Rasing and van Kampen 2000, p. 601). The bursa, the enthesopathy, and a small part of the biceps tendon insertion were resected and tests on these sections showed no signs of inflammation, indicating that the process was not active. Rasing and van Kampen (2000) hypothesised that the repetitive trauma caused by pronation and supination movements whilst using a screwdriver could have caused this. This might have been in conjunction with a pre-existing large tuberosity, or purely the result of progressive ossification of the tendon insertion, thus causing impingement and pain (*ibid.*).

Some cases of Dupuytren's contracture have been associated with enthesopathy formation. Dupuytren's contracture is a condition that causes the fingers, primarily the ring or little finger, to be pulled into flexion (Dandy and Edwards 1999). Clinically the condition has been found to be more common in men, it can run in families, and is associated with diabetes, epilepsy, and alcoholism (*ibid.*). As with most of the other conditions discussed in this section, it mainly affects middle-aged or elderly individuals (Resnick and Niwayama 1995e). There is also a strong genetic link, with an autosomal dominant inheritance pattern, but trauma (including occupationally related injury) has been implicated in a number of cases (*ibid.*). The pathologic alterations occur at either the palmar fascia, the subcutaneous tissue, or the palmar aponeurosis (*ibid.*). Despite this confusion over which soft tissues are affected, the

process itself seems to be known. The collagen matrix increases in amount and is transformed into nodules, cords or bands and can become disoriented compared to the original tissue (*ibid.*). Contracture occurs as the original tissue is replaced and this effect is made more severe by a change in material properties, causing normal use of the hand to stimulate fibrous tissue formation, thereby worsening the contracture (*ibid.*).

Enthesopathies found on the phalanges in some cases of Dupuytren's contracture are thought to be traction spurs, *i.e.* bone spurs caused by mechanical stress (Thurston 2002). All spurs were found on the ulnar-volar aspect of the middle phalanx of the little finger, the attachment site of *flexor digitorum superficialis* (Abrahams, *et al.* 1998). This muscle has the action of flexing the middle phalanges of the fingers, but not the thumb (Stone and Stone 2000). According to Thurston (2002), the enthesis at this site is probably fibrocartilaginous, but this would mean that a normal enthesis would be smooth and well-circumscribed on skeletal remains and, from personal observation (see Figure 4.1), this does not appear to be the case. This is also the shaft of the bone, at which point fibrous entheses are more common (Benjamin, *et al.* 2002).

Figure 4.1 Middle Phalanges showing the attachment of the *flexor digitorum superficialis*.



However, this does not mean that there is not a fibrocartilaginous portion of the enthesis (Milz, *et al.* 2001), thus enabling spur formation, as described by Moriggl *et al.* (2001). Thurston (2002) proposed that the formation of these spurs on the phalanges was caused by bone formation, rather than metaplasia of fibroblasts (which would occur in the soft tissue). In support of this he cites Wolff's law, *i.e.* that bone remodels due to stress. In support of this, Thurston described the angle of the spur itself, which seems to follow the angle of the fibres attaching to it. He proposed that this could be caused by stress being transferred from the fibres to the bone, rather than indicating fibre ossification (Thurston 2002). This is corroborated by Rufai *et al.* (1995) who concluded from their study of the Achilles tendon enthesis that the findings were most compatible with the hypothesis that constant strain on the enthesis leads to the formation of new fibrocartilage, which then becomes bone by endochondral ossification.

In summary, enthesopathy formation in the upper limb is probably multifactorial in origin. Age, overuse injury, disease, and genetic predisposition have all been implicated as factors. Early stages of enthesopathy formation are probably increased cortical thickness and increased prominence of the enthesis, as described by Jiang *et al.* (2002).

4.3.4 Bone Spur Formation: causes in the lower limb

This sub-section will only focus on papers linking repetitive physical stress to lower limb enthesopathy formation. This section will focus on two of the most common enthesopathies in the lower limb, Achilles tendon and plantar fascia enthesopathy. Both of the affected entheses occur on the calcaneus. It has been estimated, from radiological studies, that as many as twenty-five percent of the population has either Achilles or plantar fascia enthesopathies, many of which are asymptomatic (Benjamin, *et al.* 2000). For example, in Haglund's deformity, the presence of an exostosis on the superior tuberosity of the calcaneus is often associated with tendon and periosteal fibrocartilage degeneration (Benjamin and Ralphs 1997).

Achilles tendon enthesopathies occur on the posterior surface of the calcaneus (Milz, *et al.* 2002). The Achilles tendon is the common tendon of the *gastrocnemius* and *soleus* muscles (Gray 1974), which both have the effect of plantar-flexing the foot (Stone and Stone 2000). The tendon is approximately fifteen centimetres long and has its origin around the midpoint of the lower limb, but it receives fibres on its anterior surface almost to its end (Gray 1974). The insertion of the tendon into bone occurs at "*the posterior tuberosity on the middle third of the posterior surface of the calcaneus*" (Rufai et al. 1995, p. 585).

The occurrence of Achilles tendon enthesopathies, as with many other enthesopathies, increases with age (Benjamin, *et al.* 2000; Rufai 1995). However, there do not appear to be any papers describing a correlation between Achilles tendon enthesopathies and repetitive trauma. Nevertheless, Achilles tendonitis (inflammation of the tendon) has been linked to physical stress (Hart, *et al.* 1995). Hart *et al.* (*ibid.*) found that overuse injuries triggered chronic inflammation and led to fibrosis of the structure causing it to lose its normal mechanical properties. It is possible that this plays a role in enthesopathy formation.

Enthesopathies also occur in the plantar fascia, called the plantar aponeurosis by some authors (Akfirat, *et al.* 2003; Gibbon and Long 1999; Roger and Grenier 1997). In this review this region will be referred to as the plantar fascia, to avoid confusion, but it should be noted that the anatomy of this region is not simple, *i.e.* there are multiple structures (Abreu, *et al.* 2003; Cornwall and McPoil 1999). In general terms, the plantar fascia inserts at the medial tubercle of the calcaneus (Abreu, *et al.* 2003; Akfirat, *et al.* 2003; Cornwall and McPoil 1999), although other authors' opinions (Gibbon and Long 1999) differ stating that it attaches to the medial and lateral inferior tubercles. Further discussion of the anatomy of this zone, and the formation of the spurs will be undertaken after a review of case studies of enthesopathies at the attachment of the plantar fascia.

Many authors have linked enthesopathies at the plantar fascia with obesity (Akfirat, *et al.* 2003; Kumai and Benjamin 2002; Riddle, *et al.* 2003; Sadat-Ali 1998). Sadat-Ali

(1998) studied the incidence of plantar heel spurs among security force personnel in Saudi Arabia. Of one hundred and nine patients with heel pain, seventy-one had an enthesopathy on the calcaneus (it is unclear from the paper whether plantar spurs and Achilles heel spurs were counted together); this is an incidence of sixty-five percent. Radiographs taken of the spurs showed changes that related to the duration of heel pain. Sharp spurs were found in those individuals with a short period of symptoms, while those whose symptoms had continued for over six months had blunted spurs. Quetelet body mass index was calculated (body weight in kilograms, divided by height in meters squared, kg/m^2) and obesity was defined as >25 kg/m^2 with normal ranging from 20-25 kg/m^2. Most of the patients were obese, according to this definition. Obesity has two effects on the foot; firstly, it increases impact loads when walking or running and secondly, elasticity in the heel pad is decreased in obese individuals (*ibid.*). Footwear was also a common factor, as all individuals were wearing firm soled shoes (*ibid.*). One of the treatments for heel pain is soft shoe inserts for the heel of the shoe (Cornwall and McPoil 1999; Sadat-Ali 1998). Consequently, the author (Sadat-Ali 1998) concluded that improper footwear compounded the effect of obesity on enthesopathy formation.

There is, however, one important reservation about this paper (*ibid.*). A control group without heel pain or history of foot trauma was found to compare weight, but this control group was not imaged for enthesopathies. Heel spurs are, however, exceptionally common even in individuals without heel pain or other symptoms (Abreu, *et al.* 2003; Akfirat, *et al.* 2003; Benjamin, *et al.* 2000); consequently, it is difficult to judge the real effect of obesity or footwear on heel spur formation.

Plantar fasciitis, inflammation of the plantar fascia and the surrounding structures, is a common condition in athletes and in the obese, as well as in those with seronegative spondyloarthropathies or rheumatoid arthritis (Akfirat, *et al.* 2003). Akfirat *et al.* (2003) compared a number of features, such as plantar fascia thickness, ultrasonographic evidence for rupture, and calcaneal spurs in two groups of individuals. The first group consisted of 25 patients with idiopathic plantar fasciitis, and a second group of 15 individuals without symptoms of plantar fasciitis. Plantar

fasciitis was diagnosed on the basis of tenderness on the medial tubercle of the calcaneus (Akfirat, *et al.* 2003). No statistically significant relationship was found between plantar enthesopathies in individuals with idiopathic plantar fasciitis and those who were completely asymptomatic. However, idiopathic plantar fasciitis was thought to be caused by similar factors to plantar enthesopathies, *e.g.* overuse injuries, microtears, and repetitive stress (Akfirat, *et al.* 2003). Consequently, it is difficult to understand why no significant increase in incidence of enthesopathies was found in this study.

Gibbon and Long (1999) also undertook ultrasound analysis of the plantar fascia. The authors assessed the origin of the plantar aponeurosis in 48 asymptomatic volunteers and the appearance was compared to that in 190 patients with idiopathic plantar fasciitis, 52 with inactive plantar fasciitis, but with an active, predisposing disease (seronegative spondyloarthropathy, and rheumatoid arthritis), and 80 patients with Achilles tendon or other ankle injuries. This review will not dwell on the soft tissue findings of this study, but bone changes will be discussed (see also Section 4.2.3). The authors (Gibbon and Long 1999) found that calcaneal spurs were found in two percent of the controls, in 45 percent of those with idiopathic plantar fasciitis, in 18 percent of those with a predisposing disease, and in 1.8 percent of individuals with ankle injuries or Achilles tendon disease (these percentages do not necessarily reflect the true incidence of these spurs because of the difficulties of visualising this region of the foot using ultrasound; *ibid.*). The most common location of these spurs was at the antero-inferior border of the calcaneus, at the position at which it is crossed by the plantar aponeurosis. Importantly, the aponeurosis attaches at this point and over a large area proximal to it. Consequently, the authors hypothesised that the spur was not caused by traction, in which case it would arise from the entire enthesis, but is instead a buttress. This hypothesis will be discussed in more detail in the conclusion to this section.

Abreu *et al.* (2003) studied magnetic resonance images, radiographs, palaeopathological examples, and human cadaver feet to study the locations of plantar calcaneal enthesopathies in relation to muscle, tendon and ligament attachments. The

study demonstrated that not all enthesopathies were located in the same position, indicating that structures other than the plantar ligament are involved in enthesopathy formation. Two types of enthesopathy were found, the first extending along the longitudinal axis and the second in an oblique and lateral direction. The authors concluded that these latter ones were related to the *abductor digiti minimi*, and were probably caused by tensile forces. Five different attachment locations were also identified: the entheses of the *abductor digiti minimi*, and *flexor digitorum brevis*, between the plantar fascia and the previously stated muscles, within the plantar fascia, and at the enthesis of the short plantar ligament. No enthesopathies were identified at the *abductor hallucis* enthesis directly, but this muscle might have been associated with their formation in other locations, *e.g.* between the plantar fascia and the other muscle attachments.

Histological study of four of the cadaver feet demonstrated that the plantar fascia contained areas of degeneration, but that there was no inflammatory tissue surrounding the enthesopathies (Abreu *et al.* 2003). A zone of cartilage proliferation was present in two of the specimens at the insertion of the plantar fascia. It is probable, but not specifically stated in the text, that these two cases involved enthesopathy formation between the plantar fascia and the *abductor digiti minimi* and *flexor digitorum brevis* entheses.

The final case study to be discussed concerned the presence of plantar calcaneal enthesopathies in elderly human cadavers (Kumai and Benjamin 2002). Seventeen plantar fascia entheses from the subcalcaneal surface, including the whole medial tuberosity, were removed from one limb of elderly (64-97 years of age), embalmed cadavers. Radiographs were taken, and then histological slides were made. Eight individuals had radiographically detectable spurs, while a further three had microscopically visible spurs (the specimens were initially chosen based on preservation and lack of obvious foot abnormalities, rather than on the presence of enthesopathies; clinical histories were not known). The larger of the radiographically visible spurs showed evidence of increased cortical bone thickening. This was demonstrated both radiographically and histologically. All radiographically visible

spurs had significantly (calculated using a Student t-test) greater mean plantar fascia thickness than either those with microscopic spurs or those without spurs. According to the authors (Kumai and Benjamin 2002), the enthesopathies occurred deep to the plantar fascia on its dorsal side and were, therefore, not embedded within the plantar fascia itself.

The enthesopathies were separated from the plantar fascia by a fatty or fibrous tissue, which was rich in both blood vessels and nerves, while on the plantar surface there was a pad of unmineralised fibrocartilage. All the spurs, whatever their size, had an irregular surface of bone, an indication of active bone turnover. Evidence of two types of ossification was present on the spurs; intramembranous ossification was present on the outer and dorsal surface, and chondroidal ossification was present on the plantar aspect. There was no evidence of endochondral ossification and mineralised fibrocartilage on the surface of the spur was only rarely present (no incidence given by Kumai and Benjamin 2002).

The authors (Kumai and Benjamin 2002) noted both normal and abnormal enthesis morphology at the plantar fascia attachment. In normal cases, the enthesis of the plantar fascia was rich in fibrocartilage and typical of a fibrocartilaginous enthesis (*i.e.* four zones could be distinguished and the mineralised and unmineralised sections were separated by a tidemark, or in some cases a number of them). Muscle fibres from the *flexor digitorum brevis* were also attached at the dorsal region of the enthesis. The subchondral plate was generally thin. Abnormal changes found included cartilage cell clusters, longitudinal fissures, and localised erosion of the subchondral plate. Primarily, these changes occurred in the dorsal region of the enthesis fibrocartilage.

According to Kumai and Benjamin (2002), the location of these spurs, coupled with evidence of their formation in patients whose plantar fascia had been surgically released (a technique used to relieve heal pain), indicated that they were not caused by traction. These authors proposed two hypotheses for their formation. Firstly, they could be an adaptive response to changes in loading patterns caused by wear and tear. Secondly, they form to change loading patterns to minimise damage. According to the

authors (Kumai and Benjamin 2002), both hypotheses are compatible with the evidence so far.

Several case studies of plantar calcaneal enthesopathies have been reviewed. However, there are a number of important differences in the evidence presented, *e.g.* the location of the spurs, and the conclusions drawn regarding their aetiology. These differences will be discussed below.

The location of the enthesopathy is, probably, the most important discrepancy because the underlying anatomy must be fully understood before the causative factors can be determined. There are a number of structures arising from the plantar surface of the calcaneus which could have a role in enthesopathy formation. These structures are: the long plantar ligament, *flexor accessorius* (also called the *quadratus plantae* and the plantar head of the *flexor digitorum longus* (Platzer 1978)), *abductor digiti minimi abductor hallucis*, and *flexor digitorum brevis* (Abrahams, *et al.* 1998), as well as the plantar fascia. It can clearly be seen from the names of the structures that they have different roles, from stabilising the joints to flexion and abduction. Therefore, the location of the enthesopathy may represent differing stresses. Only Abreu *et al.* (2003) discussed the possibility that these muscles (but not *flexor accessorius*), as well as the fascia, could be related to enthesopathy presence on the plantar surface of the calcaneus. However, it is possible that the studies involving dissections, rather than just imaging, are accurate in the location of the enthesopathies in relation to soft tissue structures. This is because the soft tissues themselves can be distinguished under these conditions more readily than when radiographic techniques are used.

The cause of enthesopathies on the plantar surface of the calcaneus has been attributed to a number of factors including: poor shoe soles (Cornwall and McPoil 1999; Sadat-Ali 1998), obesity (Kumai and Benjamin 2002; Sadat-Ali 1998), and increased age (Kumai and Benjamin 2002). Disease can also cause their formation, and it is possible that many of the heels with calcaneal spurs were from individuals with undiagnosed disease. In the case of the study by Kumai and Benjamin (2002) the examined individuals had no clinical histories; only cause of death was known. Therefore, it is

possible that some of the enthesopathies were related to disease rather than overuse. Despite this fact, the authors seemed convinced that these enthesopathies were not caused by disease. Disease might not be the only possible cause as it has been suggested that some individuals naturally form bone (Rogers, *et al.* 1997). and therefore, mechanical factors might not be primary.

From the case studies discussed above, no direct link has been found between mechanical stress and the occurrence of enthesopathies. In fact, plantar fasciitis, an inflammation of the plantar fascia, has been linked to overuse (Riddle, *et al.* 2003), but no correlation was found between it and enthesopathy formation. Unlike Achilles tendon enthesopathies, the histology and position of the spurs indicates that they are not caused by traction (Gibbon and Long 1999; Kumai and Benjamin 2002). Abreu *et al.* (2003), on the other hand, concluded that the spurs were caused by traction, but they were found in so many different positions that it is possible that a number of different causes, including traction, should be considered. One of these could be similar to the role of osteophytes in osteoarthritic joints, as hypothesised by Kumai and Benjamin (2002), or that they act as buttresses (Gibbon and Long 1999). To determine aetiology more conclusively, further research is required.

4.3.5 Articular cartilage: changes in osteoarthritis

Osteophytes, also called osteochondrophytes (Menkes and Lane 2003) and chondro-osteophytes (Nishida, *et al.* 2001), are spurs of bone which form at the margins of synovial joints. They are thought to support the joint, providing a method of redistributing loads across the joint (Menkes and Lane 2003) and widening the weight-bearing portion of the joint (Nishida, *et al.* 2001). However, there is no consensus regarding their role or what causes their formation. They are found in individuals with osteoarthritis, but can also occur without osteoarthritic changes, in which case they are often age-related (Menkes and Lane 2003). Due to the similarities between hyaline cartilage and fibrocartilage, as outlined in Chapter 2, it is possible that a comparison between the occurrence of osteophytes and enthesopathies (at least bone spurs) will provide useful information regarding the formation of the latter.

Osteophytes are caused by the generation of a chondrophyte, a spur formed of cartilage, which then calcifies ((Peng, *et al.* 2000; van den Berg 1999). *i.e.* endochondral ossification typical of, for example, fracture callus (Nishida *et al.* 2001). However, it has been proposed (Middleton, *et al.* 1995) that intramembranous ossification also occurs and that the mode of ossification is dependent on the part of the osteophyte in question. These authors found that at the periosteal side of the osteophyte, ossification occurred by intramembranous ossification from mesenchymal cells in the fibrous tissue overlying bone. This was also found to occur at the outer edge of cartilage where active osteoblasts were found. This is supported by research which suggests that the periosteum at the marginal tissue surrounding the joint is the location of "repair" responses, such as osteophyte formation (Allard, *et al.* 1990).

The position of the chondrophyte is determined by the penetration of a capillary from the subchondral bone through the layer of deep cartilage (Nishida, *et al.* 2001). This is comparable to the capillary found at the centre of a bone spur type enthesopathy (Benjamin, *et al.* 2000). Histological studies of osteophytes demonstrate a central core of bone capped by a layer of fibrocartilage and hyaline cartilage (Nishida, *et al.* 2001).

The triggering factors for osteophyte formation are not fully understood. However, it is thought (Hashimoto, *et al.* 2002) that there is a biochemical trigger emanating from chondrocytes in the synovial joint leading to the vascular invasion by the capillary, which causes further chondrocyte production around the capillary. Chondrocyte hypertrophy and apoptosis (cell death) are triggered by nitrous oxide (NO) production (Hashimoto, *et al.* 2002; Nishida, *et al.* 2001) and followed by the mineralization of the matrix, creating the osteophyte. What triggers the initial biochemical action (*i.e.* loading history or biochemistry) is not known. For this reason using osteophyte formation as a model for enthesopathy formation has only limited uses.

4.3.6 Stress and Spur Formation

From the case studies above it can be seen that enthesopathy formation is not caused by physical stress alone. Other factors, such as disease and age also play a part. Current research has not yet determined the full role of each of these factors. What

does seem clear from the articles discussed above is that enthesopathies form in the direction of pull. This is probably unsurprising as their formation is intimately linked with the soft tissue attached to the enthesis. Consequently, the direction of the spur cannot be used to conclude that pull on the enthesis causes the spurs to form. What is notable is that some spurs only arise from a small portion of the enthesis. It is possible, as postulated by Gibbon and Long (1999) that they act as buttresses, thereby distributing load over a larger area. It is also possible that they only form in a small area because force is concentrated in this area because force distribution is not uniform over an irregular surface (Hirschberg, *et al.* 2000). This section will focus on two hypotheses of enthesopathy formation: firstly, that they are traction spurs, and secondly, that they are not caused by traction. It should be noted that these are not necessarily competing theories, as each theory might be applicable to different situations.

Only one of the authors (Thurston 2002) discussed in the sections above has been found to conclude that enthesopathies are traction spurs. Other authors (Abreu, *et al.* 2003; Rufai 1995) have proposed that they are caused by tensile forces or strain (it is unclear whether these authors have used these terms in their strict mechanical sense). Those authors (Gibbon and Long 1999; Kumai and Benjamin 2002) that have concluded that enthesopathies are not traction spurs, but instead act as buttresses, all studied the plantar fascia. Both papers concluded, from the location of the spurs (which do not cover the entire enthesis) that these spurs are not caused by pull from the plantar fascia, but instead act as a buttress (or other similar mechanical device) to strengthen the bone. Kumai and Benjamin (2002) also proposed that they might have a similar role to osteophytes in osteoarthritis, *i.e.* that they have a stabilising effect.

Tissue failures are common in the soft tissues, but they can also occur through or near the enthesis (Woo, *et al.* 1988). The different locations of the injuries are often classified separately, but it is possible that one injury can affect one or more of the different tissues (*ibid.*). The most common failures are in the midsubstance of the tissue, followed by those that fail by bony avulsion (*ibid.*). This is probably related to the difference in strain rates in the different substances. Studies (*ibid.*) have indicated that they are two-fold higher at the insertion site, compared to the midsubstance. It has also been found that parts of the tendon that are subject to friction, compression or

torsion are not only avascular, but also have a tendency to calcify (Benjamin and Ralphs 1997). This would affect the strain rate in the tissue.

As stated above, these differences are not mutually exclusive. Kumai and Benjamin (2002) noted that spurs at the Achilles enthesis and the plantar enthesis form by different methods of ossification. An Achilles tendon enthesopathy is formed by endochondral ossification ((Rufai 1995), whereas plantar enthesopathies form by intra-membranous and chondral ossification (Kumai and Benjamin 2002) This might be an indicator that they form in response to different types of stress and have different roles. Consequently, Achilles tendon enthesopathies might be traction spurs, whereas plantar fascia enthesopathies might be buttresses. However, there is one flaw with this argument and that is that the spurs that form on the plantar surface of the calcaneus have been found to arise from the many different structures that attach to this section of bone (Abreu, *et al.* 2003). Consequently, the location of the spurs noted by Gibbon and Long (1999) and Kumai and Benjamin (2002) is probably caused by the effect of having so many different vectors of stress acting in the same region caused by the many structures which attach at this point. Future research needs to resolve the mechanical and anatomical aspects of enthesopathy formation, meaning that finite element analysis (or other form of stress analysis) of these locations, combined with detailed anatomical analysis on normal and abnormal bones (*i.e.* bones with enthesopathies) is probably the only method of resolving these problems.

4.3.7 Cortical defects and articular cartilage

For this reason it is necessary to review changes to articular cartilage in the most common disorder affecting it, *i.e.* osteoarthritis. The characteristic features of osteoarthritis (OA) are cartilage degeneration, synovial membrane degeneration, osteophyte formation and subchondral plate thickening (Martel-Pelletier 1998).

Two types of injury can affect the articular cartilage: loss of matrix molecules or mechanical trauma (Buckwalter, *et al.* 1988). According to Buckwalter and colleagues, loss of matrix molecules can occur due to trauma to the synovial membrane, infection, inflammatory disease, long-term joint immobilisation, and some

anti-inflammatory drugs. These authors (Buckwalter, *et al.* 1988) state that this can stimulate proteoglycan degradation or suppress proteoglycan synthesis. This can be repaired if the cause is terminated rapidly enough, but it is unclear when this ceases to be possible. Mechanical trauma can also cause matrix degradation and so, in some cases, the two types of injury can overlap.

Mechanical trauma, as defined by Buckwalter and colleagues can either be blunt trauma, *e.g.* injury, abrasion, and abnormal loading, or penetrative trauma, *e.g.* laceration or osteochondritis dissecans. Blunt trauma is a common articular cartilage injury, often associated with fractures of either the bone or cartilage. Loading above physiologic levels causes cartilage swelling, and increase in collagen fibril diameter, and the alteration of the extra-cellular matrix environment. Where fissures or fractures of the cartilage occur the injury and repair response is the same as that of penetrating injuries. The actual repair response to these injuries is highly dependent on a variety of factors and is not fully understood.

Penetrative injuries have been studied in rabbits but it is unclear whether this is a good model of the repair response in humans (Buckwalter, *et al.* 1988). As with the blunt trauma injuries the location and depth (whether it crosses into subchondral bone) affects the repair response (Buckwalter, *et al.* 1988). According to Buckwalter and colleagues, those lesions that are restricted to the articular cartilage and do not penetrate the subchondral bone, are analogous to osteoarthritis. This section will closely follow their description of osteoarthritic changes, and laceration injuries that do not extend into the subchondral bone, followed by a discussion of lacerations that extend into the subchondral bone.

Early osteoarthritic changes begin in the superficial layer of the articular cartilage with fraying of the collagen fibres (Buckwalter, *et al.* 1988). These fibres are orientated along the line of the articular surface. Tears penetrate through these in vertical lines, which create vertical defects in the articular cartilage. Other changes to the superficial layer include the loss of proteoglycans, especially in the interterritorial regions. Chondrocytes proliferate in response to this and increase their production of proteoglycans. However, the chondrocytes and proteoglycans are held in place by the extra-cellular matrix and, consequently, cannot fill the gap or gaps created by the

defect. This means that the defects are not repaired and can grow. With this growth of the defect more fibres become frayed and chondrocytes die. This leads to the articular cartilage becoming thinner. Finally, it wears down to the subchondral bone. This can be witnessed in skeletal remains as joint eburnation: a shiny, smooth surface (Rogers and Waldron 1995).

Full thickness tears have been studied in rabbits (Buckwalter *et al.* 1988). These authors found that smaller tears often healed better than larger ones. The initial healing process began in the first forty-eight hours with fibrin clot formation in the defect. After five days fibroblasts and collagen fibres, orientated parallel to the articular surface, were present. The fibroblasts began to transform into cartilage by metaplasia after two weeks; at this time the extracellular matrix began to contain proteoglycans. After one month, almost all the fibroblasts had been converted into chondrocytes. By six months the injury-zone appeared normal; there was a zone of calcified cartilage overlying a zone of subchondral bone, both of which were at the same level as the uninjured zones. However, changes began to occur after six months. The proteoglycan content of the extracellular matrix in the healed zone had decreased significantly. Fibrillation and erosive changes were found in fifty percent of cases and the repair tissue had decreased in thickness. Similar changes were found after one year. The biomechanical properties of repaired tissue have been found to be inferior to normal tissue. This could be the cause of the accelerated wear patterns seen in these cases. In the case of experimental laceration (undertaken on rabbits), these lesions do not continue down to the subchondral bone (Buckwalter, *et al.* 1988). It is possible that this is because the lacerations are cut straight so that the fraying of the tissue does not continue, as occurs in fabric (personal observation).

The break-down of the cartilage matrix, which leads to fibrillation, fissures and the disappearance of the joint space, is probably related to the elevation of matrix metalloproteases and in particular the sub-groups collagenases, stromelysins and the gelatinases (Martel-Pelletier 1998). The activity of the molecules is controlled by specific tissue inhibitors. However, the important inhibitors have not been fully narrowed down, according to this author. Catabolic processes are thought by Martel-Pelletier (*ibid.*) to be caused by proinflammatory cytokines which have been found in pathological tissues. These chemicals are probably first produced in the synovial

membrane and are diffused into the joint space via the synovial fluid. This causes the chondrocytes to over-produce proinflammatory cytokines. The inorganic free radical nitrous oxide (NO) might also promote cartilage catabolism and levels of both nitrite and nitrate (chemical by-products) have been found to be increased in the synovial fluid of osteoarthritic patients.

Buckwalter and colleagues believe that the biochemistry of the healed cartilage could be the cause for the inferior tissue quality. It was found that, although the cartilage did appear to be hyaline, it was still composed of approximately thirty percent type I collagen (this is the primary component of tendon). This is probably caused by the process of metaplasia. Chondrocytes have to be of the correct phenotype to produce the "correct" kind of collagen and matrix. In the case of the matrix, the chondrocytes should synthesize large proteoglycans, but the chondrocytes which form collagen type I (like those in tendon and ligament) synthesize small proteoglycans. The abnormal composition of the extracellular matrix probably contributes to the increase in wear and tear exhibited by these healed joint surfaces.

It is not known whether thickening of the subchondral plate initiates, or is involved in, the progression of OA (Martel-Pelletier 1998). The thickening of this tissue might be caused by the healing of microfractures in the trabecular structure, which in turn leads to remodelling to resist the stresses causing these fractures. The thickening of the subchondral bone generates a stiffer area, which is a poor shock absorber compared to subchondral bone of normal thickness. Or the thickening might be related to generalised bone thickening related to the increased bone mineral density found in osteoarthritic patients. Martel-Pelletier (*ibid.*) also proposes that abnormal osteoblasts might additionally affect cartilage metabolism. These abnormal cells might be involved in accelerating the subchondral bone formation, which would then increase the mechanical pressure (because of the stiffer bone) on the overlying joint surface. This would then trigger the deterioration and degeneration of joint cartilage.

Where articular cartilage often presents with longitudinal fissuring with clusters of large rounded cells at the fissure margin, similar findings occur in fissured fibrocartilage (Benjamin and Ralphs 1997). Unlike articular cartilage, signs of repair occur in the enthesis fibrocartilage and radiographs of this region often show signs of

calcification. These authors demonstrated that, histologically, these abnormalities are filled with amorphous metachromatic material or disorganised fibrous extracellular matrix.

Another common defect occurring at articular cartilage is osteochondritis dissecans (OD), also called "König's disease; post-traumatic subarticular necrosis; transchondral fractures" (Aufderheide and Rodríguez-Martín 1998, p. 81), which is a non-inflammatory condition of the convex surfaces of synovial joints (Aufderheide and Rodríguez-Martín 1998). It should be noted that Aufderheide and Rodríguez-Martín (*ibid.*) are the only authors to write that the condition is limited to convex surfaces; the very fact that it can occur on the distal tibial articulation and the glenoid fossa (Bui-Mansfield 2002) indicates that this is, in fact, not the case. However, all authors agree that OD is limited to the articular epiphysis. I propose that these lesions also occur at fibrocartilaginous entheses.

Osteochondritis dissecans is a term used for an osteochondral fracture (Bui-Mansfield 2002); these fracture fragments can be either present *in situ*, or partially or completely detached. These fragments can consist of either cartilage or cartilage and bone (Resnick, *et al.* 1995).. Histologically, the cartilage can be hypertrophied, with or without laminar calcification and the subchondral bone is normally avascular with evidence of repair. These fragments can lead to a loose body in the joint (Bui-Mansfield 2002; Ortner 2003b). The osseous lesion on the joint surface can close over with a thin layer of bone, but remains visible as a depression on the bone surface (Ortner 2003). Osteochondritis dissecans (Bui-Mansfield 2002) is a special case of osteochondrosis, special in that it is limited to the articular epiphysis.

The onset of OD occurs from childhood to middle age, but is most common in adolescence (Resnick, *et al.* 1995). Children under the age of ten are rarely involved, although those that are, are normally obese (Aufderheide and Rodríguez-Martín 1998). Men are typically more frequently affected than women (Resnick, *et al.* 1995). However, more recent studies (Bui-Mansfield 2002) indicate that there is no sex predilection. Patients can be asymptomatic but pain can occur along with limited movement, clicking, locking, and swelling (Resnick, *et al.* 1995). These lesions are normally unilateral (*ibid.*) and, in the long term, OD can lead to osteoarthritis (Bui-

Mansfield 2002). Table 4.4 lists common sites of OD.

Table 4.4 Common sites of OD, according to Resnick *et al.* (1995).

Extremity	Site	Comment
Upper extremity	Glenoid cavity	
	Head of the humerus	
	Elbow	(typically the capitulum of the humerus)
	Wrist	Most commonly on the scaphoid in "*bakers, boxers, pelota players, acrobats, and pneumatic drill workers*" (Bui-Mansfield 2002).
Lower extremity	Femoral condyles	Most common
	Patella	Typically it occurs in the medial facet and middle or lower portion of the bone only
	Talar trochlea	Middle third of the lateral border or the posterior third of the medial border
	Tibia	
	Bones of the tarsus	
	Acetabulum	

Trauma is probably the most common cause, although it has been proposed that there is an inherited component, which is possibly autosomal dominant (Resnick, *et al.* 1995). These genetic cases are associated with '*short stature, endocrine dysfunction, Scheuermann's disease, Osgood-Schlatter's disease, tibia vara, and carpal tunnel syndrome*' (Resnick *et al.* 1995, p. 2611). Moreover, these authors also note that it may occur in subadults because of irregularities of ossification. Despite these findings, it is thought that the most common cause is trauma to the site, in the form of an osteochondral fracture caused by abnormal forces at the joint (Resnick, *et al.* 1995). Bui-Mansfield (2002) proposes that the trauma leads to abnormal levels of compressive stress at the articulation, thus causing the fracture.

In around fifty percent of cases of femoral condyle OD, clinical history indicates trauma as being the main cause. Trauma is also the most likely cause of patella OD, as indicated by its association with ligament laxity and lateral patella subluxation (Resnick, *et al.* 1995). In addition, these authors state that this is also a common site

of pain, often associated with knee flexion, especially under loading. They also describe talar lesions as being caused by foot inversion. Inversion of the foot leads to the compression of the talar trochlea against the fibula; if this inversion continues, the lateral collateral ligament ruptures resulting in an avulsion of a fragment from the talar trochlea. The medially located lesion is also thought to be traumatic in origin, resulting from plantar-flexion of the foot with simultaneous inversion and subsequent rotation of the tibia on the talus. Consequently, there is consensus both clinically and experimentally that trauma is the most likely cause of this lesion, but the mechanism is unknown (Resnick, *et al.* 1995). However, there is no histological consensus (*ibid.*), and it has been proposed that trauma alone is not the cause; ischaemia is also required at the location.

Bui-Mansfield (2002) described three stages of the pathology of this lesion: Stage 1, the acute injury, involves thickening and oedema of the intra- and peri-articular soft tissues. In Stage 2 the contour of the epiphysis appears irregular with a thinning of the subcortical bone. Micro-fractures in the trabeculae lead to incompetent blood vessels in the epiphysis, resulting in poor healing. The final stage is the reparative period, when scar tissue replaces the dead tissues. At this stage the dead bone loses structural support, leading to a flattening of the articular surface. Healing can be hindered further by the influx of synovial fluid into the lesion which creates a subchondral cyst (Bui-Mansfield 2002).

Differential diagnosis of femoral condyle OD is spontaneous osteonecrosis, but this occurs predominantly in older patients and tends to involve the weight-bearing area of the medial femoral condyle (*ibid.*). In the patella "*chondromalacia patella, dorsal defect of the patella, and osteochondral fractures*" (*ibid.*, p. 2619) should be considered, whereas in the glenoid cavity it could be the result of a developmental defect (Bui-Mansfield 2002); this has the appearance of a small focal defect at the centre of the glenoid cavity. Unlike OD, there is no associated bone marrow oedema. OD is also normally eccentrically located and larger than this defect.

4.3.8 Cortical Defects: Calcific Tendonitis

This sub-section focuses on cortical defects caused by calcific tendonitis. Calcific tendonitis is a painful condition (Wolf 1999) in which calcium salts are deposited in the substance of tendons at the point where the blood vessels arising from the musculature and the bone communicate (Resnick 1995b). Although the apatite crystals only rarely cause symptoms at this stage (Anonymous 2000), they can grow and cause pressure on, or grow into, other structures, such as bursae, thus causing pain (Resnick 1995b). At the shoulder this is a common cause of pain, especially in individuals between 30 and 50 years of age (Wolf 1999). Very little else is known about this process, although the rapid onset of the condition, without a history of trauma, does imply that it has a different aetiology from degenerative conditions, such as impingement syndrome (*ibid.*). In some cases the acute (painful) stage of the condition is triggered by a generalised illness or an operation (Anonymous 2000).

Dürr *et al.* (1997) described a case of calcific tendonitis with cortical erosion at the insertion of the *pectoralis major*. The 31-year-old patient had no history of trauma or other diseases, but had had pain in the left upper arm for four weeks. A radiograph demonstrated calcification at the insertion of the muscle. A later CT (computer tomography) scan showed a calcified mass next to the cortex with an underlying erosive lesion which extended into the bone marrow (*ibid.*); this occurred at the lateral lip of the distal portion of the bicipital groove, presumably at the enthesis. MRI scans, after the administration of a contrast dye (gadolinium diethylenetriamine penta-acetic acid or Gd-DPTA), showed a region of increased dye uptake surrounding the lesion, as well as within the bone marrow. A biopsy revealed a thickened cortex and histology demonstrated fibrocartilage with calcification and chronic inflammation. Blood tests revealed an elevated white blood cell count and C-reactive protein levels, indicating inflammation and/or infection (Anonymous 1997-2003). Radiographs were taken three months later by which time the patient had no symptoms and the lesion had gone (Dürr, *et al.* 1997).

Other authors (Kraemer and El-Khoury 2000) have also described cases of calcific tendonitis in which cortical erosion occurs. None of the cases described by Kraemer and El-Khoury (*ibid.*) was associated with previous trauma, but all six cases of cortical erosion were associated with powerful muscles; five cases were located at the insertion of the *gluteus maximus*, while one was located at the insertion of the *pectoralis major*. Calcific tendonitis without cortical erosion, on the other hand, most commonly involves the *supraspinatus* tendon, which is weaker than those discussed above. Calcific tendonitis itself is most common in sedentary females between the ages of forty and seventy. Calcific tendonitis of the *supraspinatus* tendon is reported to be associated with systemic diseases, such as diabetes and thyroid disorders and with HLA-A1. However, it is unclear whether this association occurs in calcific tendonitis with cortical erosion. Calcific tendonitis is only rarely symptomatic and has been discovered as an incidental finding on radiographs; in fact, it has been estimated that only ten percent of cases of calcific tendonitis of the *supraspinatus* tendon are ever symptomatic (*ibid.*). These facts certainly have implications for epidemiological studies. For example, the association of the condition with sedentary females between 40 and 70 years of age might be an artefact of other factors, *e.g.* social factors affecting doctor's visits.

The "disease" (if it is a disease) process in calcific tendonitis goes through three stages, according to Kraemer and El-Khoury (2000). The first stage cannot be viewed radiographically as it involves no additional calcium deposits. In the *supraspinatus* tendon there is a portion of the tendon, approximately 1.5 centimetres proximal to the enthesis, which is vulnerable to both hypoxic and mechanical stress (called the critical zone or Codman's critical portion) (Kraemer and El-Khoury 2000; Uhthoff and Sarkar 1991). According to Kraemer and El-Khoury (*ibid.*), during the first stage this undergoes fibrocartilage transformation (presumably via metaplasia, although this is not specified in the article). Secondly, the fibrocartilage becomes replaced with a calcium salt deposit; this stage can be seen radiographically. Microscopic examination demonstrates multifocal deposits of calcium, which are interrupted by strands of either fibrocartilaginous connective tissue or damaged tendon fibre (Uhthoff and Sarkar 1991). At this stage resorption can also occur, taking the form of phagocytosis by macrophages and giant cells; this can occur either during the formation of the

deposit or subsequently. The final stage occurs when the deposit has been fully resorbed leaving a void that becomes filled with granulation tissue, which then matures leaving a scar. This stage ends once new collagen fibres have been formed and become aligned to those in the rest of the tendon. The resorptive stage can occur spontaneously, according to Uhthoff and Sarkar (*ibid.*). For this reason the authors suggest that the process should be considered reactive as opposed to dystrophic calcification.

Calcific tendonitis can also occur in the tendon of the *longus colli* muscle and has been called calcific prevertebral tendonitis, calcific tendonitis of the *longus colli* muscle and retropharyngeal calcific tendonitis (Mihmanli, *et al.* 2001). In the case of a 57 year-old female described by Mihmanli *et al.* (*ibid.*), the typical inflammation of the tendon had spread to the body of a neighbouring vertebra. In this case, it was hypothesised by the authors that the inflammation had been carried through the bloodstream from the tendon to the bone. As with the cases discussed above there was no history of trauma, and both zones of inflammation were resolved quickly after the administration of non-steroidal anti-inflammatory drugs and did not recur.

In a retrospective analysis of fifty cases of calcific tendonitis, it was found that seventy-eight percent of cases had associated cortical erosion (Flemming, *et al.* 2003). It should be noted that, according to Flemming *et al.* (*ibid.*), cortical erosions can be difficult to pick up on radiographs, and therefore it is possible that some cases were missed and that cases have also been missed by other studies. Cortical erosions are probably, according to these authors, caused by an inflammatory response to calcium hydroxyapatite deposition at an enthesis (*ibid.*). In tendons associated with powerful muscles this may produce a focus of hypervascularity leading to localised bone resorption and the mechanical forces associated with these muscles may exacerbate the effect (*ibid.*). The authors note that even after calcific tendonitis has resolved, the cortical erosion can remain.

Calcific tendonitis has been found in children, but seems to be rare (Sakamoto and Kozuki 2002). The case reported by Sakamoto and Kozuki (*ibid.*) involved the insertion of the *biceps brachii* tendon on the radial tuberosity. The three-year-old boy

had fallen, causing pain in his wrist, but this subsided and then resumed and spread throughout his forearm. This case did not involve cortical defects.

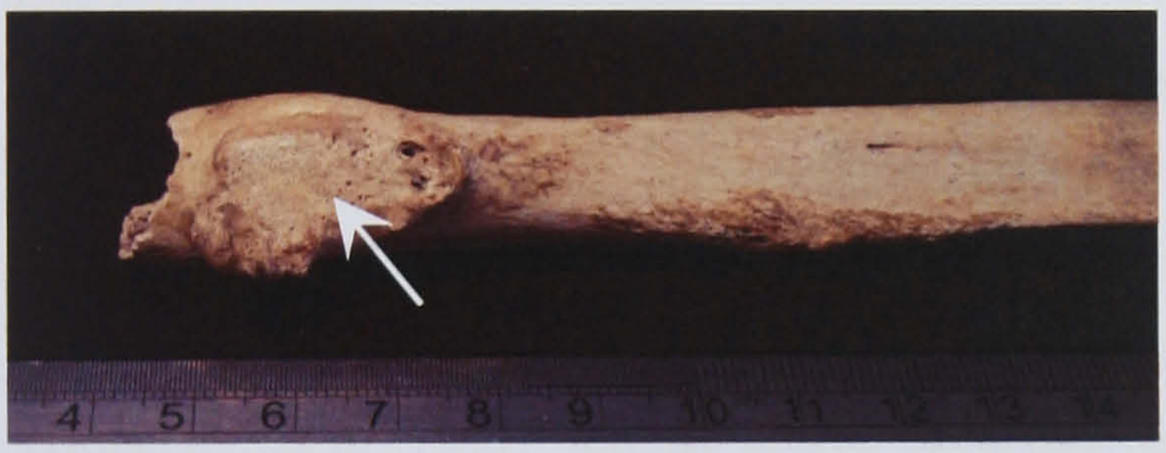
The calcium deposit, or calcium granuloma as it is called by Uhthoff and Sarkar (1991), is a focus of calcium deposit mixed with amorphous debris and surrounded and infiltrated by cells (typically macrophages, but also fibroblasts and less frequently polymorphonuclear cells). According to these authors (*ibid.*), the granulomatous appearance is caused by the multinucleated giant cells and the abundance of capillaries and small vessels surrounding the deposits. The macrophages and giant cells often contain phagocytosed substances in their cytoplasm. The calcium granuloma is typically seen in patients whose calcifying tendonitis is causing severe pain and disability.

The cause of calcific tendonitis is not known, although a number of theories have been postulated. One proposal (Flemming, *et al.* 2003) is that degeneration of the tendon is caused by recurring trauma, and local hypoxia resulting in an alkaline pH leading to crystal deposition. Currently, the leading theory, according to Flemming *et al.* (*ibid.*), is that the degeneration of the tendon is caused by its response to the crystal deposition (rather than the degeneration being the cause of the crystal deposition). Calcification itself is caused by local hypoxia at the tendon insertion, which leads to fibrocartilaginous metaplasia, and this cartilage then calcifies. However, Flemming *et al.* (*ibid.*) found that only 11 percent of cases demonstrated chondroid metaplasia. Nevertheless, it is possible, although not discussed by the authors that this is because the disease process was inactive at the time of the biopsy, *i.e.* chondroid metaplasia had ceased.

Cortical erosions were also found by Hayes *et al.* (1987). These authors studied five cases of calcific tendonitis, all with cortical erosions. The affected sites were: the tendon of the *gluteus maximus* (two cases), the tendon of the *pectoralis major* (two cases), and the tendon of the *adductor magnus* (one case). The authors did not state where the affected sites were exactly, but from the figures it seems that they were the proximal femur [attachment site of both *gluteus maximus* and *adductor magnus* [(Abrahams, *et al.* 1998)] and the proximal humerus [attachment site of *pectoralis major (Abrahams, et al. 1998)*]. Woven bone was present in one case of cortical

erosion and the authors (Hayes, *et al.* 1987) hypothesised that this was a repair response to the erosive lesion (see Figure 4.2 woven bone at an enthesis). They also postulated that the cortical erosions were caused by an increase in local vascularity and active inflammation at the insertion site or that it was a result of pressure. However, this latter theory was not fully described. They also noted the possibility that these tendons were affected because their critical zones might lie close to the bone or that mechanical pull from these powerful muscles might be involved. Uhthoff and Sarkar (1991) note that pressure from the humeral head in calcific tendonitis of the *supraspinatus* muscle exacerbates the fibrocartilaginous metaplasia within the muscle.

Figure 4.2 Woven bone at a *biceps brachii* insertion, without a known cause.



Currently, calcific tendonitis is thought to occur in around three percent of the population (Flemming, *et al.* 2003). Not all cases of calcific tendonitis lead to cortical defects, as a retrospective study of fifty cases demonstrated (*ibid.*). However, the authors found that seventy-five percent of cases did involve cortical defects. It has also been found that cortical defects remain after calcific tendonitis has resolved (*ibid.*), although in other cases the lesion has been found to resolve with the resolution of the tendonitis (Dürr, *et al.* 1997). Consequently, lesions of this type in archaeological populations cannot be attributed to an active disease at death. As will be seen below there are also other causes of cortical defects, but distinguishing them in skeletal remains may prove impossible.

4.3.9 Cortical Defects: Acute

Tendons and ligaments often tear away a small piece of bone, rather than breaking away at the union of hard and soft tissues (Haines and Mohuiddin 1968). For this reason, the models of healing, described in section 2.2, involving surgical injury at the interface, are not necessarily wholly applicable to natural scenarios of injury. Avulsion injuries are common in childhood, and in these cases entire apophyses can be pulled away from a bone (Micheli and Fehlandt 1992; Resnick, *et al.* 1995). However, they can also occur in adults, especially in those with lower then normal bone mineral density (Wren, *et al.* 2001). This section on avulsion injuries is included in this review because of their association with overuse injury.

Avulsion injuries in children often occur at apophyses, protuberances of bone to which tendons are attached. In general, apophyses have a small window of time when they can be avulsed, and this period begins when the associated muscle becomes strong enough to generate the required forces, and ends a little after physeal fusion (Donnelly, *et al.* 1999). Similar results have been found in experimental studies on rabbits. The failure mode of rabbit ligaments has been found to be directly linked to maturation, such that rabbits with open epiphyses suffered avulsion injuries, whereas those with closed epiphyses had mid-substance tears of the ligament (Franck, *et al.* 1988). Another study on rabbits demonstrated that prior to epiphyseal fusion the failure of the medial collateral ligament involved the avulsion of a portion of tibia (Woo, *et al.* 1988). Once fusion occurred, only twelve percent (4 out of 34) failed by avulsion. Franck and colleagues (1988) explained this on the basis that the strength of the ligament-bone junction varies with age, whereas Woo and colleagues (1988) explained these findings on the basis that the enthesis is affected by growth plate activity. It is likely that the cause of this variation is regulated by the growth of the individual and the requirement for the enthesis to "migrate" along the bone to maintain its correct anatomical location. Once fusion has occurred the enthesis location is fixed. This probably explains the rarity of muscle tears in children (Radin 1993).

Common sites of avulsion in children are: '*the iliac crest* [...], *anterior superior iliac spine* [...], *anterior inferior iliac spine* [...], *ischial apophyses* [...], *and lesser trochanter* [...]' (Donnelly *et al.* 1999, p. 140). These authors describe other common sites occurring at the knee and on the humerus. Radiographic detection of these avulsions is possible and seen as displacement of the apophysis with associated periosteal bone formation ((Donnelly, *et al.* 1999). These injuries can be caused by either a single event of tensile stress, or from overuse injuries (*ibid.*).

Overuse injuries occur with repetitive microtrauma to a tissue whose injury outpaces its ability to repair (Micheli and Fehlandt 1992). This type of injury only rarely occurs in children who do not take part in organised sports, according to these authors. In one study of children with apophysitis or tendinitis there were no cases of apophysitis (0 out of 724) caused by "free play", *i.e.* all cases were caused by stresses experienced during organised sports training (*ibid.*). In the sample studied by these authors, apophysitis was found to be most common during the growth spurt. The authors propose that this is because of the loss of flexibility during this period, thereby increasing forces across the joint. This is combined with weakening of the apophysis, caused by the rapid increase in chondrocytes at the physis. It should be noted that all individuals studied had a history of training errors, although what these included was not stated.

Avulsion injuries in adults have been found to correlate with decreased bone mineral density (Wren, *et al.* 2001). Achilles tendons and associated calcaneal insertions were taken from human cadavers. The bone mineral density was calculated using dual-energy X-ray absorptiometry and samples were randomly (irrespective of age) assigned to fast or slow strain rate tests to assess the amount and type of stress (*i.e.* static or active) causing failure of the system. It was found that the most significant factor in the type of injury induced was bone mineral density and that the age of the individuals was not significant. However because of the common decrease in bone mineral density in elderly individuals avulsions were more common in this group. Tendon ruptures were more common in the younger individuals. The strain rate, simulating static versus dynamic loading, had no significant effect on the type of

injury sustained in these examples. This study demonstrated that the tendon maintains its mechanical properties better in maturity than bone. The location of these lesions also relates to the density of calcified tissue. It has been found that tendon avulsions frequently include a flake of bone and occur at sites in the upper limb that have less calcified tissue than at other sites (Benjamin, *et al.* 1992). However, this was just an incidental finding that was not fully studied by the authors.

Biomechanical tests have shown that the tendinous portion of an enthesis has better elastic and viscous properties than that of the bony end (Thomopoulos, *et al.* 2003). This is because of the well-organised collagen fibres, and the presence of mechanically important proteoglycans. Effectively, this means that the tendinous zone can withstand greater tension over a longer duration than that of the bony zone of the insertion. In combination with this, peak strain seems to be "concentrated" at the bony end of an enthesis, such that experimental peak strain was three times as high at the bony end as it was at the tendinous end (*ibid.*). This is probably caused by the relative disorganisation of the collagen fibres at the bony end of the enthesis. The disorganisation of the fibres at the bony insertion probably means that stresses cannot dissipate along direct pathways, thus effectively "concentrating" them in one place.

Apophyseal avulsion injuries have been found in archaeological samples (Formicola, *et al.* 1990; Maat and Mastwijk 2000). However, as can be seen from the case studies, these are unlikely to be the cause of the pits or lytic lesions recorded as MSM because of their anatomical location. This is unfortunate as avulsion injuries are one of the few cases of injury that can be attributed to physical stress and few other factors have to be taken into account (excepting age at injury). However, the cases of avulsion injuries in adults, involve flakes of bone ripping off with a tendon. Such injuries have been found in the upper limb and particularly occur at sites which have less calcified tissue. It is possible that some of the sites at which lytic lesions are found, might be caused by these types of injuries. Future research should involve the mapping of the occurrence of lytic lesions in skeletal remains to determine whether there is a pattern. If a pattern exists then this should be compared to the amount of calcified tissue present at each site and the characteristics of these lesions should be compared to

radiographs of these lesions from a clinical setting. This should determine whether the lytic form of MSM are caused by avulsion injuries and thereby help to determine their aetiology.

4.3.10 Cortical Defects: Miscellaneous

This sub-section includes cases not caused by calcific tendonitis or avulsion injuries. As with the previous two sections, the focus of this section will be on case studies. Conclusions drawn from these will be discussed in Section 4.3.12.

Bone changes at the greater tuberosity of the humerus have been found in cases of rotator cuff tears (Jiang, *et al.* 2002). According to these authors, the changes range from pitting and erosion to hyperostosis and enthesopathy. It was found that degenerative changes, such as those outlined above, were found on 20 percent (2 out of 10) of intact shoulders, 86 percent (6 out of 7) of partially torn shoulders and 100 percent (5 out of 5) of fully torn shoulders and that these changes increased in severity from the intact shoulders to severe examples in the fully torn shoulders (*ibid.*). The authors also found an age correlation for these changes, although considering the sample size (22 individuals) this should be viewed with caution.

The rotator cuff comprises a group of muscles (*supraspinatus, infraspinatus, teres minor, and subscapularis)*, which protect the head of the humerus from dislocating while the more powerful muscles act upon the joint (Stone and Stone 2000). Rotator cuff tears can be either partial or full, but probably begin as partial tears of the *supraspinatus* tendon from whence the tear spreads into other structures (Pollock, *et al.* 1995). According to Pollock *et al.* (*ibid.*), these tears are multifactorial in origin, *i.e.* repetitive trauma is not the sole cause. Studies on cadavers have even shown that trauma causes rupture everywhere except at the entheses, indicating that this trauma is not the primary cause (*ibid.*). It is possible, however, that changes associated with death, decomposition and body storage (*e.g.* embalming, freezing) affect the results of this type of study.

Some authors (Ogata and Uhthoff 1990) have hypothesised that these tears are caused by intrinsic factors alone. However, according to Pollock *et al.* (1995), this cannot explain why these tears always start at the same place. Mechanical factors might explain this. It has been discovered that contact between the inferior surface of the acromion and the *supraspinatus* tendon occurs proximally on the tendon at zero degrees of humeral elevation (*ibid.*). This shifts distally on the tendon until between sixty and one hundred and twenty degrees contact is maximised and is located in the region of the insertion (correlating with the site of damage described above) (*ibid.*). Intrinsic factors also play a role. Acromion morphology and spurs also affect contact and can probably increase the likelihood of rotator cuff tears (*ibid.*).

Tension in the *supraspinatus* tendon could also lead to tears. It has been found that with the arm in abduction some tendon fascicles (those located nearest the articular surface) are in tension, and lax fascicles were found in that region further away from the articular surface (*ibid.*). Consequently, by loading the arm whilst in abduction, the tendon can begin to rip through the fibres that are in tension.

The most common feature associated with rotator cuff tears is the age of the individual (Jiang, *et al.* 2002; Levitz and Iannotti 1995). Levitz and Iannotti (*ibid.*) found that most individuals with rotator cuff tears were over 40 years of age. Rotator cuff tears are also more common in individuals who repeatedly perform tasks at shoulder level. The risk is further increased if these tasks involve static loading of the shoulder (Andersson 1995) It is, however, unclear whether repetitive trauma throughout those 40 years, or more recent trauma [the biomechanical properties of tendon change with age (Woo and Young 1991)] is the cause of this finding. It is also unclear whether trauma accelerates the disease process or just causes symptomatic presentation of an already degenerated rotator cuff (Levitz and Iannotti 1995). Levitz and Iannotti (*ibid.*) also point out that any relationship between overuse injury and age-related phenomena is unclear because work pressures may just draw attention to age-related degenerative changes.

A radiographic study demonstrated that in the early stages of rotator cuff tears, the bone on the greater tuberosity, at the enthesis of the *supraspinatus* tendon, often

appears more prominent (Jiang, *et al.* 2002). As the condition develops this region is subject to degenerative changes, such as pitting and erosion, as well as hyperostosis and cortical thickening (*ibid.*). In their study of the trabecular microstructure of the greater tuberosity in cases of rotator cuff tears, the authors found a link between age and enthesopathy formation. Another study found enthesopathy formation in an autopsy sample, but in a retrospective analysis of patients' clinical history, no evidence of a previous shoulder complaint was found (Uhthoff and Sarkar 1991).

Other cortical irregularities have also been described on the humerus. Pseudotumour deltoideus is a cortical irregularity at the deltoid tuberosity which can either take the form of a thickened and irregular cortex or be an expansion of the tuberosity with lucency when viewed radiographically (Morgan, *et al.* 2001). Although some of the cases described are symptomatic, *e.g.* painful, this is not true of all of them. Differential diagnoses of this irregularity were considered by the authors; these included: calcific tendonitis with cortical erosions, burned out neoplasms, accentuation of the normal deltoid tuberosity, herniation pits, and avulsive cortical irregularities. No calcific deposits were found in the tendon, nor were there cases from subadults. Consequently, both calcific tendonitis with cortical erosions and avulsive cortical irregularities were ruled out. Burned out neoplasms were ruled out because the radiographic findings and the age groups affected did not match. Herniation pits were also ruled out by the authors, as they occur at articular capsule attachments. However, in many respects they are very similar; both anomalies are associated with lucency on radiographs, and can be either symptomatic or asymptomatic, but pseudotumour deltoideus occurs at an enthesis and not the attachment of the articular capsule (Morgan, *et al.* 2001). For these reasons the authors proposed that pseudotumor deltoideus is an example of normal variation at the deltoid enthesis on the humerus and is characterised by having a smooth, well-defined outline on radiographs and can be associated with or without pain.

Herniation pits can also occur on the femoral neck and are characterised by a subcortical cavity resulting from fibrocartilaginous tissue growing into the bone through a site of cortical erosion (De Paulis, *et al.* 1998). According to the authors,

these occur due to major physical activity. However, the exact meaning of this is unclear.

Plantar fasciitis can also cause erosion on the bone. In four percent (out of 190) of cases studied by Gibbon and Long (1999) with idiopathic plantar fasciitis, erosions were found at the enthesis of the plantar aponeurosis. This might have reflected an early stage of seronegative spondyloarthropathies (SpA), or it might have been caused by long-standing repetitive stresses affecting this zone (*ibid.*).

4.3.11 Stress and Cortical Defects

There are numerous causes of cortical defects. However, in the osteological literature, these seem to have not been studied. It is clear that in many cases of lytic enthesopathies, one of these processes must have been involved. As these are all linked, in some way, to trauma; cortical defects are perhaps the best hope for studying activity using MSM. For this reason, further studies are required which bridge the gap between clinical and osteological cases, so that a lesion diagnosis guide can be created from the location of the lesion and its appearance.

4.3.12 Conclusions

The effect of trauma on the soft tissues, enthesis and bone appears to have the effect of weakening it when subjected to further traumatic incidents. This indicates that entheses and subchondral bone are perfect sites for studying activity-related changes, but only if the activity involves incidents which cause these traumatic onslaughts. From the clinical literature on occupational physical stress, it is clear that many everyday activities (if performed regularly enough, and by susceptible individuals) will cause these types of injuries. Therefore, the study of MSM in biological anthropology is of importance. However, there are clearly not enough epidemiological studies in the clinical literature which allow lesions at entheses to be compared between known clinical cases and archaeological cases. For this reason, the study of

MSM should be put on hold until further research has been undertaken to solve this problem.

Chapter 5. Factors Affecting the Development of Enthesopathies at Attachment Sites: Disease

5.1 Introduction

The aim of this chapter is to introduce, and describe diseases which cause enthesopathy formation for the purposes of considering differential diagnoses to activity-related stress. Table 5.1 lists possible differential diagnoses. The diagnostic criteria discussed in this section will be used in Chapter 6 to avoid pooling skeletons with possible diseases, with those without. The secondary aim of this section is to clarify and extend (where possible) the diagnostic criteria used by palaeopathologists to diagnose those diseases discussed. This will be achieved through a review of clinical literature of these diseases (focussing on skeletal rather than soft tissue changes).

Table 5.1 List of causes of enthesopathy formation adapted from Cush and Lipsky (2001, p. 1332).

Disease category	Disease name	Comments
Inflammatory	Rheumatoid arthritis (RA)	
	Ankylosing spondylitis (AS)	
	Reiter's syndrome (ReA)	
	Psoriatic arthritis (PsA)	
	Inflammatory bowel disease (EA)	
	Lyme disease	
	Late-onset pauciarticular juvenile arthritis	
	Leprosy	
Mechanical / degenerative	Trauma	See Chapter 4
	Osteoarthritis	
Metabolic / endocrine	Diffuse idiopathic skeletal hyperostosis (DISH)	
	Acromegaly	
	Fluorosis	
	Retinoid therapy	Not discussed in this review, as it is unlikely to have occurred prior to modern drug therapy.
	Hyperparathyroidism	
	Hypothyroidism	

Disease category	Disease name	Comments
	Polyneuropathy, organomegaly, endocrinopathy, M-protein and Skin changes (POEMS) syndrome	
	X-linked hypophosphatemia	

For most of the diseases discussed in this chapter, palaeopathological diagnostic criteria exist (Aufderheide and Rodríguez-Martín 1998; Ortner 2003b). However, clinical literature can provide information on rare manifestations of diseases, manifestations (such as enthesopathies) that are of limited diagnostic value, on new understandings of disease aetiology, and current prevalence rates.

Perhaps the most significant disadvantage is that individuals appear to react differently to the same stimuli, due to intrinsic (*e.g.* genetic) or extrinsic (*e.g.* environmental) factors. In the case of the spondyloarthropathies, these differences have led to the apparent under-diagnosis of the disease (Boyer, *et al.* 1997; Dougades, *et al.* 1991; Stafford and Yousse 2002). This is a problem for both clinical and palaeopathological research. Clinical literature that describes skeletal change in disease is primarily based on radiological analysis. However, skeletal changes can be missed radiologically or these changes may be asymptomatic and therefore not looked for radiologically. Consequently, skeletal manifestations of disease may not appear in clinical literature, even though they are seen during palaeopathological analysis. Disease manifestations or virulence may also have changed over time and could have affected bone reaction in the skeleton (Roberts and Manchester 2005). Clinical research into disease often focuses on those symptoms or signs that are most distressing to the patient or are most likely to cause serious complications. Unfortunately, this can mean that research sidelines observations of skeletal changes. This affects the data available for palaeopathologists to use for diagnosis of skeletal lesions. Using clinical data to determine palaeopathological diagnostic criteria must consider these factors. Nevertheless, the limitations discussed above do not out-weigh the benefits of focusing on clinical data in this review.

5.2 Seronegative Spondyloarthropathies

Seronegative spondyloarthropathies (SpA) are a spectrum of diseases that affect the synovial joints, bursae, tendon sheaths, entheses, soft tissues and bones. Unlike patients with rheumatoid arthritis (RA), those with SpA do not have antibodies to IgG molecules (rheumatoid factor) (Resnick and Niwayama 1995d). However, many patients have the HLA-B27 antigen in their blood which is part of the human major histocompatability complex (Resnick and Niwayama 1995d). Diseases falling into this category (SpA) are: ankylosing spondylitis (AS); psoriatic arthritis (PsA); reactive arthritis (ReA); enteropathic arthritis (EA); undifferentiated spondyloarthropathy (uSpA); synovitis, acne pustolosis, hyperostitis, osteitis syndrome (SAPHO syndrome); sternocostoclavicular hyperostosis; and chronic multifocal recurrent osteomyelitis (CMRO) (Fournié 2004). Other authors disagree as to whether Whipple's disease (a disease of the bowel) should be included (Arnett 2001). Moreover, some authors (Keats 1999) do not include SAPHO syndrome, sternocostoclavicular hyperostosis or CMRO. Behçet's disease, according to Keats (*ibid.*), should never be included. However, this chapter will follow the standards of Fournié (2004).

There is a consensus that the SpA are under-diagnosed clinically (Boyer, *et al.* 1997; Dougades, *et al.* 1991; Khan 2002; Rothschild and Woods 1991). These authors do not agree on the reasons for this. Khan (2002) and Dougades *et al.* (1991) have hypothesised that the spectrum of disease is wider than previously thought (see Sub-section 2.1). The other authors have proposed that the "classic" case of "bamboo spine" and sacroiliitis (typical for AS) has misled doctors into thinking that these are diagnostic criteria. This review concludes that both groups are correct. There is a wider spectrum for the disease, and more subtle changes are necessary for their diagnosis. Recognition of the early stages of these diseases also requires recognition of these subtle changes.

This was highlighted by an epidemiological study undertaken by Boyer *et al.* (1997). These authors studied two groups of patients: one with diagnosed SpA and the other with back pain and other hallmarks of the disease. It was found that females were

most frequently under-diagnosed, but there was generalised under-diagnosis. Those misdiagnosed often had atypical disease. However, it was previously thought that males were more commonly affected than females (with a ratio of 10 to 1). This ratio has now been revised to 3 to 1 (*ibid.*). This demonstrates a pitfall of using an individual's sex to diagnose disease in palaeopathology.

Recent studies (Uppal, *et al.* 2005) have also demonstrated that there are differences in clinical expression of diseases between different "ethnic groups". This study demonstrated that Middle Eastern patients (from Kuwait and nearby Arab states) were more likely to have ankylosing spondylitis, whereas those from Southern Asia (primarily from the Indian subcontinent) tended to have uSpA. Peripheral arthritis was less common in the Middle Eastern group. In general the current prevalence of SpA is thought to be approximately 0.3 percent (Lories, *et al.* 2005).

5.2.1 General Clinical Diagnostic Criteria

General diagnostic criteria differ from disease characteristics, in that diagnostic criteria are those features of the disease spectrum used to provide a diagnosis and differential diagnosis. It has been recognised, recently, that there is a need, in clinical contexts for a list of diagnostic criteria for the spondyloarthropathies, as a whole, to avoid problems of misdiagnosis particularly in those individuals with less aggressive forms of SpA, as discussed above. The European Spondyloarthropathy Study Group (ESSG) criteria (Dougades, *et al.* 1991) (see Table 5.2) stress the importance of multiple indicators in the diagnosis of the SpA spectrum. The authors (*ibid.*) found both false positives and false negatives when these criteria were applied to clinical cases. However, these criteria performed well compared to the diagnostic criteria for single diseases (*e.g.* AS) within this spectrum. Many of these criteria are also used in the Amor criteria for SpA (Amor, *et al.* 1990; Saraux, *et al.* 2002) (see Table 5.3). In this system each symptom, sign, radiographic finding and blood test result are given weighted points that are added together to provide a score. The primary advantage of the ESSG criteria over Amor's criteria is the more limited range of diagnostic symptoms needed for diagnosis. It is, however, questionable whether either of these

criteria can be used in the early diagnosis of SpA, as neither of them included early cases in their samples (Amor, *et al.* 1990).

Table 5.2 Diagnostic criteria for the seronegative spondyloarthropathies, adapted from the European Spondyloarthropathy Study Group Criteria (ESSG) (Dougades *et al.* 1991).

Symptoms	Definitions	Comment
Inflammatory spinal pain	History/current symptom of spinal pain in dorsal or cervical region with at least four of the following: a) onset before age 45 b) insidious onset c) improvement with exercise d) association of pain with morning stiffness e) minimum 3 months duration	
OR		
Synovitis	History/current symptom of asymmetric arthritis or mainly lower limb arthritis	
AND One or more of the following symptoms:		
Positive family history	History of disease (ankylosing spondylitis, psoriasis, acute uveitis, reactive arthritis, or inflammatory bowel disease) in either first-degree or second-degree relatives	
Psoriasis	History/current symptom as diagnosed by a physician	
Inflammatory bowel disease	History/current Crohn's disease or ulcerative colitis diagnosed by a physician and confirmed by radiography or endoscopy	
Urethritis, cervicitis, or acute diarrhoea	Occurring within one month before arthritis	
Alternating buttock pain	History/current pain alternating between right and left gluteal areas	
Enthesopathy	History/current spontaneous pain or tenderness at examination of the site of the insertion of the Achilles tendon or plantar fascia	

Symptoms	Definitions	Comment
Sacroiliitis	Bilateral grade 2-4 or unilateral grade 3-4 according to the following radiographic scale: 0 = normal 1 = possible 2 = minimal 3 = moderate 4 = ankylosis	Revised grading system based on MRI findings defines these grades as [adapted from (Hermann and Bollow 2004)]: 0 = without chronic inflammatory changes. 1 = subchondral sclerosis, without blurring of joint contours; less than 2 erosions per slice; normal joint space retained. 2 = retention of normal joint cavity space; more than 2 erosions per slice; subchondral sclerosis with max. 1/3 of joint contours blurred. 3 = subchondral sclerosis with more than 1/3 of the joint contours obscured; AND/OR pseudodilations of the joint space by marginal erosions; AND/OR bone buds forming "bridges" along with narrowing of the joint cavity. 4 = Ankylosis of more than ¼ of the joint space; joint space filled with "fat marrow-like tissue.

Table 5.3 Diagnostic criteria for the seronegative spondyloarthropathies, adapted from Amor (Amor *et al.* 1990). The disease is declared to be a SpA if the number of points from the 12 criteria is equal or greater than 6.

Category of signs etc.	Signs, symptoms etc.	Points
Signs or clinical history of:	Nocturnal lumbar or spinal pain with or without lumbar or spinal morning stiffness	1
	Asymmetric oligoarthritis	2
	General buttock pain, buttock pain on rocking	1 or 2
	Dactylitis (manifesting as sausage digits) fingers or toes	2
	Heel pain or other enthesopathy	2
	Iritis	2
	Non-gonococcal urethritis or cervicitis less than a month before the onset of arthritis	1
	Diarrhoea less than a month before the onset of arthritis	1
	Presence or prior history of psoriasis and or balinitis and or chronic enteritis	2
Radiologic signs	Sacroiliitis (grade ≥ 2 bilateral or grade ≥ 3 unilateral)	3
Genetic	Presence of the antigen B27 and or family history of pelvospondylitis, Reiter's syndrome, psoriasis, uveitis, chronic enteritis	2
Sensitivity to treatment	Relief of the pain within 48 hours of taking non-steroidal anti-inflammatory drugs (NSAIDs) and or rapid recurrence of pain once treatment with NSAIDs ceases (within 48 hours)	2

The HLA-B27 antigen cannot be used as a diagnostic criterion, because of its varying frequency in different racial and sexual groups (Cattaneo 1991; Evison, *et al.* 1999) and because not all patients with a seronegative spondylarthropathy have this particular antigen (Khan 2002; Ramos and Lopez de Castro 2002; Stafford and Yousse 2002). However, the latter authors have proposed that this antigen contributes to the severity of the disease.

It should be noted that neither the ESSG nor the Amor criteria are suitable for direct application to skeletal samples, because of their reliance on patient and family history, and the presence of pain. However, with some modification (as will be discussed in Section 5.2.4) the ESSG criteria could become a useful tool in palaeopathology.

5.2.2 Enthesopathy Formation and Description of Enthesitis

Peripheral enthesopathy is a clinical hallmark of SpA and may be seen in all forms (Erdem, *et al.* 2005). There have recently been speculations concerning the primary lesion location in SpA. Some authors have hypothesised that the disease initially affects the entheses leading to enthesitis, from whence the inflammatory response progresses to the synovium (Benjamin and McGonagle 2001; Laloux, *et al.* 2001; McGonagle, *et al.* 1998; McGonagle, *et al.* 2002a; McGonagle, *et al.* 2002b). Other authors disagree, concluding that synovitis is the primary lesion (Brandi, *et al.* 2001; François, *et al.* 2001; François, *et al.* 2000). It has also been hypothesised (Maksymowych 2000) that there is an autoimmune reaction to cartilage in general, but especially to fibrocartilage [note that fibrocartilage is not that different to hyaline cartilage (Benjamin and Ralphs 2004)].

Based on imaging studies, McGonagle *et al.* (1998) proposed that enthesitis was the primary abnormality to appear in SpA. The authors hypothesised that from the enthesitis lesion, pro-inflammatory cytokines and growth factors are released into the synovium causing synovitis. This hypothesis explains two other typical features of SpA: dactylitis and extra-articular symptoms. Dactylitis involves the thickening of the fingers and toes. There are many entheses along the bones of both the fingers and toes and the joint capsules (insertions of joint capsules are also considered entheses by

some authors, for example, Braun *et al.* 2000) of the interphalangeal joints that are in part composed of the tendons of the flexor and extensor muscles (Milz, *et al.* 1998). Consequently, McGonagle *et al.* (1998) proposed that digital swelling is probably caused by an initial enthesitis lesion leading to synovitis and soft tissue swelling. This is borne out, according to the authors, by the imaging evidence of pencil-in-cup deformities of the distal interphalangeal joint. In these, the cup is probably caused by the calcification of the distal capsule with erosion of the flexor or extensor tendon enthesis. Periostitis and erosion adjacent to the joint capsule are also seen radiographically, indicating that the inflammation is not limited to the synovial joint. Supporting evidence for this hypothesis can be gleaned from the extra-articular signs common to these diseases. These structures are: the root of the aorta, the wall of the aorta, the ciliary body of the eye, the skin extensor surfaces, and the lung apex. All these structures have been found to contain fibrocartilage or are subject to similar biomechanical stressing to that of the epiphyseal entheses (Maksymowych 2000; McGonagle, *et al.* 2001), *i.e.* tension and compression. According to these authors, it is likely that this biomechanical stressing of these structures is the unifying factor. Note that many of these structures are also involved in Marfan's syndrome, a disease associated with weakened connective tissue and resulting in joint dislocation and aortic root, eye and lung apex disease (McGonagle, *et al.* 2001).

Based on the above, a re-classification of joint disease has been proposed by McGonagle *et al.* (1998). Diseases such as rheumatoid arthritis, which have a primary synovial lesion, are grouped separately from those whose primary lesion occurs at the entheses. Included in the latter group are: all SpA, SAPHO (synovitis, acne, pustolosis, hyperostosis and osteitis syndrome), remitting seronegative symmetrical synovitis with pitting oedema (RS3PE), juvenile chronic arthritis and forms of osteoarthritis with entheseal abnormalities. It is also possible that inflammatory monoarthritis, Behçet's disease and Lyme disease fall into this category.

Other authors (Braun and Sieper 1999; François, *et al.* 2000) do not consider the primary SpA lesion to be located at the enthesis. They propose that the primary lesion is located in the synovium. Braun and Sieper (1999) in a letter responding to McGonagle *et al.* (1998) state that enthesitis cannot fully explain the diffuse bone involvement of sacroiliitis, nor does it necessarily agree with the finding of bacteria in

the synovial membrane of patients with reactive arthritis. Neither does it explain the effect on the subchondral bone or bone marrow (Braun and Sieper 1999). Braun and Sieper (*ibid.*) also state that McGonagle *et al.* (1998) have confused diseases that are part of the SpA spectrum with those that are not, for example RS3PE, SAPHO, Lyme disease and osteoarthritis. However, RS3PE has been shown, by magnetic resonance imaging to have an enthesis-based pathology (McGonagle, *et al.* 1999), but it is unclear whether similar studies have confirmed or refuted the claims regarding the other diseases. Imaging of entheses is difficult because of the lack of water and the fact that they are often hidden by other tissues (Braun, *et al.* 2000).

Experimental evidence has demonstrated that synovitis is the primary lesion at the sacroiliac joint in ankylosing spondylitis. François *et al.* (2000) found that in the early stages of the disease there was no evidence of enthesitis, just synovitis leading to cartilage destruction and myxoid bone marrow change. In the later stages, the joint became progressively more obliterated (the normal joint space is approximately 4mm wide, according to Hermann and Bollow 2004) and there was evidence of focal enthesitis. Consequently, these authors concluded that sacroiliitis in ankylosing spondylitis is characterised by lesions in the synovium, the subchondral bone and possibly enthesitis.

However, according to some authors (Benjamin and McGonagle 2001) the sacroiliac joint differs from many other synovial joints in that it is similar to an enthesis. This is supported, according to these authors, by radiographic evidence of sacroiliitis, which appears similar to enthesitis. Sacroiliitis is a key early feature of ankylosing spondylitis in which the changes occur primarily on the iliac side of the joint (*ibid.*). Benjamin and McGonagle (*ibid.*) proposed that this predilection is due to the different lining materials found on each side of the joint. The sacral side of the joint is lined with hyaline cartilage, whereas the iliac side is lined with fibrocartilage. With age, these differences disappear and the iliac side becomes more hyaline in character. It is possible that these age-related cartilage changes, and other age-related fibrocartilage biochemical changes, are the reason why the SpA rarely begin their disease course in anybody over forty years of age (Braun, *et al.* 2000). Sacroiliitis might also be related to shear forces characteristic of fibrocartilaginous structures (and possibly the reason for the presence of fibrocartilage). This build up of stresses and changes related to

them might explain why sacroiliitis is rarely found in children with childhood ankylosing spondylitis, despite the fact that the joint is rich in fibrocartilage during this period of life. These children often develop typical changes, including sacroiliitis, later in life (*ibid.*).

Although imaging of entheses has been difficult, recent advances in imaging techniques, along with what seems to be a burgeoning clinical interest in the SpA (based on personal observation publication rates using NCBI PubMed www.ncbi.nlm.gov/pubmed/), has provided an insight into this area. Enthesitis can be seen as blurring of compact bone, with or without the formation of irregular woven bone, which remodels into normal compact bone (Hermann and Bollow 2004). Other changes visible at entheses using radiography are: osteopenia, cortex irregularity, soft tissue calcification and new bone formation (sometimes bone erosion) (Braun, *et al.* 2000). Adjacent to the enthesis, periostitis can also be seen and, if there is soft tissue present, soft tissue swelling (*ibid.*). The underlying bone marrow can also be affected at a considerable distance from the enthesis and this can be seen as bone oedema (*ibid.*). The mechanism of enthesopathy formation has been discussed in Chapter 3. However, spurs caused by inflammatory changes are thought to be subject to further inflammatory changes, unlike those with a non-inflammatory aetiology (Niepel and Sitaj 1979).

5.2.3 Differential Diagnoses

The primary disease discussed in conjunction with SpA in clinical literature is rheumatoid arthritis (Marzo-Ortega, *et al.* 2002; McGonagle, *et al.* 1998; Resnick and Niwayama 1995d; Stafford and Yousse 2002). Rheumatoid arthritis (RA) is an autoimmune disease characterised by the presence of the rheumatoid factor in the blood, but this is not the *sine qua non* of the disease (Martin 2000). In general, this disease is a destructive arthropathy predominantly affecting small synovial joints, *e.g.* those of the hand. Destructive lesions do also occur in SpA. However in contrast, they are characterised by repair and new bone formation. Typically, the large joints and the spine are affected (Marzo-Ortega, *et al.* 2002). Enthesitis (as discussed above) is predominant in the SpA, but not a feature of RA (McGonagle, *et al.* 1998). However,

clear similarities do exist, particularly with ReA and PsA, both of which affect small joints of the hands and feet and the cervical spine. This is also the most commonly affected region of the spine in rheumatoid arthritis (Resnick and Niwayama 1995c). Table 5.4 lists diagnostic criteria for RA. These criteria are focussed on synovial joint inflammation, in contrast to the SpA which focus on spinal, sacroiliac joint and enthesis inflammation.

Table 5.4 Diagnostic criteria of Rheumatoid Arthritis [adapted from (Resnick and Niwayama 1995c)].

Criteria	Further comment
'*Morning stiffness in and around joints present for at least 1 hour before maximal improvement.*'	Should have been present for at least 6 weeks
'Soft tissue swelling (arthritis) of three or more joint areas observed by a physician'	Should have been present for at least 6 weeks
'*Swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints*'	Should have been present for at least 6 weeks
'*Symmetric swelling (arthritis)*'	Should have been present for at least 6 weeks
'*Rheumatoid nodules*'	
'*The presence of rheumatoid factor*'	
'*Radiographic erosions or periarticular osteopenia, or both, in hand or wrist joints, or in both*'	Radiographic evaluation of the feet is also suggested

In palaeopathological research DISH is the primary differential diagnosis for SpA (see Section 5.3 for further discussion). This disease process affects both the spine and entheses. Unlike the SpA, the primary spinal element involved is the anterior longitudinal ligament in the thoracic region of the spine. The calcification of this tissue has a "dripping candle wax" appearance and is completely different from spinal involvement in the SpA. Enthesopathy involvement can, in general, not be differentiated. However, in contrast to SpA, there are no further synovial joint changes and the joint space is maintained at the sacroiliac joint in DISH (Barozzi *et al.* 1998).

No other diseases cause this particular range of bony changes. However, there are many diseases causing sacroiliitis. Table 5.5 lists diseases to consider and how they differ from the SpA. Diseases and other factors causing enthesopathies have been

discussed in Section 5.1. Specific vertebral and synovial lesions are variable, based on which of the sub-diseases in the SpA spectrum is affecting the patient.

Table 5.5 Differential diagnosis of sacroiliitis (Arnett 2001; Awada, *et al.* 2003; Benchakroun, *et al.* 2004; Bosilkovski, *et al.* 2004; Kremer, *et al.* 1996; Raman, *et al.* 2004; Resnick and Niwayama 1995c).

Type of disease	Disease	Features of sacroiliitis for differential diagnosis
Seronegative Spondyloarthropathies (SpA)	AS ReA PsA Enteropathic SpA Acne associated with SpA and SAPHO Intestinal bypass-related arthritis	These are all SpA, but there are differences in expression of sacroiliitis between these individual diseases, as will be discussed in the following subsections. Specifically in ReA and PsA intra-articular fusions are rare.
Infectious	Pyogenic infections	Widening of joint space, blurring and erosions of subchondral bone progressing to spontaneous ankylosis. Psoas abscess can occur.
	Tuberculosis	Widening of the joint, retroperitoneal abscess, cartilage destruction and remodelling.
	Brucellosis	Blurring of joint space margins, narrowing/widening of joint space, subchondral erosions or sclerosis
	Whipple's disease (note this is often included in the SpA)	
Miscellaneous	Hyperparathyroidism and renal osteodystrophy	Narrowing of joint space does not occur (widening does), neither does ankylosis.
	Paraplegia, disuse	No sclerosis or ligamentous ossification, but osteoporosis
	Sarcoidosis	Rare, but generally unilateral and cannot be distinguished from other causes without a biopsy. Note that sarcoidosis can coexist with SpA (Kremer *et al.* 1996).
	Rheumatoid arthritis	Only superficial erosive lesions, minimal sclerosis, ankylosis minimal
	Osteitis condensans ilii	Only an area of sclerosis on the ilium, no other changes
	Gout	Large hollowed out lesions only
	Degenerative joint disease	Smooth subchondral margin and anterior osteophytes. Widespread ossification of the joint is rare

5.2.4 The Palaeopathological Implications

Recording of SpA in skeletal remains must take into account the clinical methods of diagnosing this group of diseases, but also bear in mind the limitations, *i.e.* the lack of soft tissue preservation. In the case of these diseases the applicable generalised diagnostic signs are: synovitis, enthesopathy and sacroiliitis. From the discussion of the clinical literature it is clear that "severe" vertebral changes, *e.g.* bamboo spine are not necessary for the diagnosis of SpA. Ortner (2003) described this general pathology as: asymetric skeletal involvement, predominantly affecting the spine, sacroiliac joints and with a prominent presence of enthesopathy. Although this is just a general description, this author feels that general diagnostic criteria (Table 5.6) should be in place to avoid misdiagnosis and under-diagnosis of SpA. The aetiology of these diseases is so poorly understood currently, that it is possible that palaeopathological studies could shed further light on the subject.

Table 5.6. New criteria based on recent clinical discussions of SpA.

Both 1 and 2 must be present
1) presence of sacroiliitis: erosions or the beginnings of bridges of bone marginal to (although this can include) the auricular surface, especially on the iliac side of this joint.
2) multiple enthesopathy formation: more than one appendicular enthesopathy
And either:
3) synovitis: seen as degenerative changes at one or more synovial joints of the appendicular skeleton
Or
4) vertebral changes (any part of the spine): these can take the form of syndesmophytes, or synovitis

Additional skeletal changes might provide sufficient criteria to determine which of the SpA has caused them, or can confirm diagnosis in cases in which one of the criteria in Table 5.6 fail: for example in ReA where sacroiliitis is rare). However, in many cases skeletal preservation is not sufficient to use these criteria. For this reason additional criteria drawn from the separate diseases are needed.

5.3 Diffuse Idiopathic Skeletal Hyperostosis (DISH)

Diffuse idiopathic skeletal hyperostosis (DISH) is characterised by the tendency for bone formation in the spine and at extra-spinal sites, specifically involving ossification or calcification of entheses. It has been known by many different names (Table 5.7.), but recently there seems to have been a consensus in the English-language literature on the name DISH. This disease is thought to occur in between 66 percent of the population of 40 years of age and up to 11 percent in individuals over 70 years of age (Mazières and Rovensky 2000). Other authors (Resnick 1985) put the prevalence at between 15 and 20 percent in an elderly population (but the age of the population is not described). In Hungary the prevalence of DISH in men aged 50-54 was ten percent but rose to 36 percent in males over 75 years of age; in females the prevalence was 1.9 percent in the younger age group, rising to 26 percent in those over 75 years of age (Kiss, *et al.* 2002). A similar prevalence was found in "whites" in a study of chest radiographs from hospitals and clinics in Minnesota, USA (Weinfeld, *et al.* 1997). Black, Native-American and Asian prevalences from the same study, in contrast, were found to be around 20 percent in individuals over 70 years of age.

Table 5.7 Synonyms for DISH.

Name	Reference
Spondylitis deformans	(Resnick and Niwayama 1995b)
Spondylitis ossificans ligamentosa	(Aufderheide and Rodríguez-Martín 1998; Resnick and Niwayama 1995b)
Spondylosis hyperostotica	(Aufderheide and Rodríguez-Martín 1998; Resnick and Niwayama 1995b)
Physiologic vertebral ligamentous calcification	(Resnick and Niwayama 1995b)
Generalised juxta-articular ossification of ligaments of the vertebral column	(Resnick and Niwayama 1995b)
(Senile) ankylosing hyperostosis of the spine	(Cammisa, *et al.* 1998; Resnick and Niwayama 1995b)
Forestier's disease	(Aufderheide and Rodríguez-Martín 1998; Resnick and Niwayama 1995b; Roberts and Manchester 2005)
Dysmetabolic hyperostosing polyenthesopathy	(Cammisa, *et al.* 1998)
Zuckergusswirbelsäule	(Cammisa, *et al.* 1998)
Coating vertebral hyperostosis	(Cammisa, *et al.* 1998)
Forestier-Rotes Querol disease	(Aufderheide and Rodríguez-Martín 1998)
Forrestier, Rotes-Querol and Ott's disease	(Cammisa, *et al.* 1998)
Dysmetabolic hyperostosing spondyloarthropathy	(Cammisa, *et al.* 1998)
Diffuse enthesopathic hyperostosis	(Aufderheide and Rodríguez-Martín 1998)
Vertebral osteophytosis	(Resnick and Niwayama 1995b)

Despite the many names and the frequency of the disease, its aetiology is currently unknown. There have been reports of the disease being associated with numerous factors: age, spinal trauma, diabetes mellitus [although no significant difference in prevalence of DISH between normal controls and patients with diabetes mellitus has been found (Sencan, *et al.* 2005), elevated environmental fluoride levels, high doses of vitamin A, type II diabetes, android or sthenic obesity, biliary stones, atheromatous vascular disorders, systemic hypertension, diseases of lipid or purine metabolism, monoclonal gammopathy and other dysgammaglobulinemias. High body mass index (BMI or weight-for-height index kg/m^2) has also been linked (Mata, *et al.* 1997) with DISH. These authors compared healthy individuals with DISH and spondylosis and found that those with DISH were heavier, had a greater BMI, greater chest expansion and waist circumference. Those individuals with DISH were also heavier in their youth with slower subsequent weight gain than either of the other groups. For this reason these authors proposed that high BMI in youth might be a risk factor for DISH. This indicates a possible future explosion in the incidence of DISH in the USA and UK where the prevalence of childhood obesity is increasing (McCallum and Gerner 2005). Another hypothesis has been proposed (Cammisa, *et al.* 1998; Resnick and Niwayama 1995b; Resnick, *et al.* 1975) that DISH is not a disease, but a state (possibly hereditary) in which the body's normal response to stimuli [such as surgery, association with other diseases (Resnick and Niwayama 1995b) or mechanical factors (Di Franco, *et al.* 2000)] is exaggerated and excess bone is formed (see Section 5.8 on ossifying diatheses).

Clinical evidence of the disease has often suggested that patients with DISH do not suffer from pain, discomfort, or decreased mobility. However, some authors (Cammisa, *et al.* 1998; Resnick and Niwayama 1995b) have proposed that this is not the case. These authors recorded patients with stiffness, restricted motion, and tendinitis. In some patients cervical dysphagia was also found (Cammisa, *et al.* 1998; Resnick and Niwayama 1995b). This is caused by prominent cervical osteophytes located adjacent to areas where the oesophagus is normally attached making these patients at high risk of aspiration and pneumonitis (Resnick and Niwayama 1995b).

A disease similar to DISH, but involving the ossification of the posterior longitudinal ligament (OPLL), is common in East Asia (Resnick 1995a). As with DISH it

commonly affects individuals between forty and seventy years of age and is twice as common in males as females (Koga, *et al.* 1998). Unlike DISH, it primarily affects the cervical spine, without extra-spinal involvement. Ligament ossification can be limited to only one or two vertebral bodies, with or without preservation of the disc space. Thoracic and lumbar vertebrae can also be affected. This condition has been found in conjunction with DISH (Sokoloff 1983). Because of the lack of involvement (or the lack of reporting) of extra-spinal entheses, this is of limited use for differentiating disease-related enthesopathy from activity-related changes in skeletal remains. This disease will not be discussed further.

5.3.1 Clinical Diagnostic Criteria and Differential Diagnosis

Clinically, spinal involvement must satisfy three criteria to allow for a definite diagnosis of DISH (Resnick and Niwayama 1995b). These criteria are:

1. 'The *presence of flowing calcification and ossification along the anterolateral aspect of at least four contiguous vertebral bodies with or without associated localized pointed excrescences at the intervening vertebral body – intervertebral disc junctions'* (Resnick and Niwayama 1995b). p. 1465).
2. 'The *presence of relative preservation of intervertebral disc height in the involved vertebral segment and the absence of extensive radiographic changes of "degenerative" disc disease, including vacuum phenomena and vertebral body marginal sclerosis'* (*ibid.*).
3. '*The absence of apophyseal joint bony ankylosis and sacroiliac joint erosion, sclerosis, or intra-articular osseous fusion'* (*ibid.*).

The fulfilment of all three criteria is necessary to establish a definitive diagnosis; they were chosen to eliminate other spinal diseases (Resnick and Niwayama 1995b), as will be discussed below. These criteria have been modified to involve only two contiguous vertebrae (Julkunen, *et al.* 1975).

DISH involves degenerative changes in the cartilage in which blood vessels from subchondral bone invade and cells in the cartilage react by becoming osteoblasts

(Cammisa, *et al.* 1998). The general radiographic appearance of changes is of horizontally orientated ossifications of the anterior longitudinal ligament (Hermann and Bollow 2004). These ossifications normally preserve the intervertebral disc space, but this can be slightly decreased (Cammisa, *et al.* 1998). The ossifications often have the appearance of flowing candle wax or downward-flowing cake icing, where the increase of ossification and more anterior location of this at the level of the disc space forms bumps (Hermann and Bollow 2004; Resnick and Niwayama 1995b).

Thoracic spine involvement occurs in 95 percent of patients (Cammisa, *et al.* 1998) and is the region most commonly the first targeted by the disease (Resnick and Niwayama 1995b). The most commonly involved vertebrae are those between T7 and T11, and the incidence of involvement decreases towards the cervical spine (*ibid.*). New bone is formed on both left and right sides of the spine, but is generally more prominent on the side opposite the aorta, or most commonly the right-hand side (*ibid.*). It should be noted that individuals with *situs inversus* (the left-right reversal of organs) have been found to have more prominent new bone formation on the left side if their aorta runs along the right side (*ibid.*). This supports the theory that the pulsation (or other attribute) of the aorta inhibits florid new bone growth (Cammisa, *et al.* 1998). New bone formation only rarely affects the posterior spine, but there can be hyperostosis of the spinous processes which can, in exuberant cases, connect adjacent processes (Resnick and Niwayama 1995b). Despite the common retention of intervertebral disc space, calcification can occur (*ibid.*). In these cases ossification often occurs in the mid-anterior or mid-lateral sections of the space and sometimes in contact with vertebral body margins (Cammisa, *et al.* 1998). In these cases there is often calcification and elongation of disc material, which radiographically appears as radiolucent areas (Resnick and Niwayama 1995b).

Involvement of cervical vertebrae leads to the characteristic "dripping candle-wax" bone formation on the vertebral bodies (*ibid.*). The thickness of the newly formed bone can be considerable, leading to a doubling of the antero-posterior diameter of the vertebral bodies (Mazières and Rovensky 2000). This hyperostosis can form elongated bony outgrowths extending from one vertebral body to another (Resnick and Niwayama 1995b), but these can be discontinuous because of their predilection for descending down the spine (*ibid.*). The most commonly affected vertebrae in the

cervical spine are C4 to C7 (*ibid.*). The posterior spine and the posterior longitudinal ligament are more commonly involved in the cervical than the thoracic spine and can lead to hyperostosis or "osteophyte" formation (*ibid.*).

In the lumbar spine, the upper portion is most commonly affected (*ibid.*). In contrast to the new bone formation in the thoracic spine, that in the lumbar spine is more focal and the bone spurs are pointy and have been likened to a "parrot beak" (Cammisa, *et al.* 1998) p. 59). However, full bridging between vertebral bodies is rare (Mazières and Rovensky 2000). These growths are often more symmetrical on the lateral aspects of the vertebral bodies than they are in the thoracic spine (Resnick and Niwayama 1995b). Posterior spine involvement is rare at this level of the spinal column (*ibid.*).

As can be seen from above, the anterior longitudinal ligament is not the only spinal manifestation of the disease. Apart from those ligaments listed above, the ligamentum flavum, joint capsules and ligaments of the posterior spinal joints, can also be affected by ossification (Mazières and Rovensky 2000).

Appendicular bone formation is common in DISH and can occur without, or with only minor, spinal involvement (Resnick and Niwayama 1995b). This could make early-stage DISH difficult, if not impossible, to diagnose in skeletal remains. Changes occur both at entheses and around the joints and take the form of enthesopathies running in line with the soft tissue fibres (Cammisa, *et al.* 1998). Para-articular osteophytes, which can lead to osseous bridging or intra-articular ankylosis, can also occur (Resnick and Niwayama 1995b). The pelvis and hip joint are commonly involved (Cammisa, *et al.* 1998). Enthesopathies of the *iliopsoas* muscle enthesis on the lesser trochanter are more common in DISH than in other bone forming disease (Resnick and Niwayama 1995b). Another characteristic lesion is the formation of a "third tibial spur" (Mazières and Rovensky 2000), p. 208) anterior to the tibial spines at the enthesis of the anterior cruciate ligament. Other entheses to be affected are: the interosseous membrane of the radius and ulna or the tibia and fibula, joint capsules of the hand and frequently the olecranon and Achilles tendon (insertion) (Mazières and Rovensky 2000; Resnick and Niwayama 1995b). Fibrous entheses, such as the deltoid, can also be affected: normally this does not appear as spur formation, but it can be seen radiographically as prominence and irregularity of the deltoid tuberosity

(insertion) (Resnick, *et al.* 1975). Hyperostotic changes can affect the clavicle, distal phalangeal tufts (in the form of their broadening) and sesamoid bones (in the form of their enlargement) (Resnick and Niwayama 1995b).

Two diseases produce similar signs and symptoms to DISH: acromegaly and the SpA. Both diseases involve spinal and extra-spinal bone formation at entheses. Unlike the SpA, osteoporosis is not a common feature of the spine in DISH (Cammisa, *et al.* 1998) and the effect of this on preservation (less mineralised bone, presumably, disintegrate more rapidly than normally mineralised bone) might be one of the reasons that DISH is found more commonly in skeletal remains than SpA (see below). The shape of the syndesmophytes in DISH is more "flowing" than that found in any of the SpA (Resnick and Niwayama 1995b), and there is more symmetry in bone formation across the vertebral bodies, when changes occur in the thoracic spine, than in DISH (Mazières and Rovensky 2000). Sacroiliitis with ankylosis of the joint is not a feature of DISH (although bone formation around the sacroiliac joint can occur) (Cammisa, *et al.* 1998). Furthermore, inflammatory lesions of the joints and entheses do not occur in DISH. If apophyseal joints are affected in DISH, it is the joint capsule, rather than the joint surface which is affected (Mazières and Rovensky 2000). Acromegaly generally involves the thickening and irregularity of long bone cortices; the skull can also be affected (Resnick 1985). Other characteristics of acromegaly which do not occur in DISH are joint space widening and premature osteoarthritis (Mazières and Rovensky 2000). Table 5.8 presents diseases that should be considered when considering differential diagnoses.

Table 5.8 Differential Diagnoses of DISH.

Disease	Differences in spinal signs	Differences in extra-spinal signs
Seronegative spondyloarthropathies	In SpA the syndesmophytes are thin and vertical, not like flowing "candle-wax". Zygoapophyseal capsule ossifications in DISH, not joint surface involvement (Mazières and Rovensky 2000)	Osseous erosion, sclerosis, irregular and poorly defined new bone formation are characteristic of the SpA (Resnick and Niwayama 1995b)

Disease	Differences in spinal signs	Differences in extra-spinal signs
Acromegaly	New bone does not resemble flowing "candle-wax"	Joint space alterations and osteoarthritis (premature) do not occur in DISH
Intervertebral (osteo)chondrosis	In DISH there are no: vacuum phenomena, disc space narrowing, reactive bone sclerosis, cartilaginous nodes (Resnick and Niwayama 1995b)	
Spondylosis deformans [degenerative disc disease; (De Maeseneer, *et al.* 1999)]	In DISH there are: ligamentous calcification and proliferative enthesopathy ((Resnick and Niwayama 1995b)	DISH: spinal and extra-spinal enthesopathies (Mazières and Rovensky 2000)
Sternoclavicular hyperostosis	Massive new bone formation in the cervical spine not found in DISH (Resnick and Niwayama 1995b)	
Hyperparathyroidism		Erosive lesions of the subchondral bone of entheses do not occur in DISH (Resnick 1985)
Idiopathic hypoparathyroidism in combination with an ossifying diathesis	Exuberant new bone formation at entheses: indistinguishable from DISH (Lambert and Becker 1989)	
Fluorosis	Increase in bone density in fluorosis, but the bone is brittle (Resnick 1985)	
Ochronosis	Anterior disc calcification and vertebral body osteoporosis do not occur in DISH (Resnick 1985)	No pigmentation of the sclera, or cartilage in DISH (Resnick 1985)
Axial neuropathic osteoarthropathy	Presence of disc space narrowing, sclerosis, subluxation leads to a disorganised look not found in DISH (Resnick 1985)	
Hypertrophic osteoarthropathy		Diaphyseal periostitis is common on almost all long bones, but not in DISH (Resnick 1985)
Pachydermoperiostosis		"Fluffy" periostitis is not common in DISH (Resnick 1985)

Disease	Differences in spinal signs	Differences in extra-spinal signs
Calcium Pyrophosphate Dihydrate Crystal Deposition Disease (pseudogout)	Destructive lesions of the vertebral bodies and disc spaces with disc calcification, and destruction of facet joints not found in DISH (Oostveen and van de Laar 2000)	Widespread tendon calcifications are not found in DISH, nor is pyrophosphate arthropathy DISH (Resnick 1985). Capsular ossification (especially of the feet and elbow) does not occur in DISH (Resnick 1985)
X-linked Hypophosphatemic Osteomalacia		Calcification of joint capsules does not occur in DISH and the commonly affected sites (hands and sacroiliac joints) significantly differ from DISH (Resnick 1985). Lower limb long bone curvature and bone reinforcement lines are also key features of this disease, but not DISH (Hardy, *et al.* 1989)

It should be noted that AS and DISH have been found to co-exist in some patients (Kozanoglu, *et al.* 2002). Although this might seem difficult to verify, these individuals actually have two forms of syndesmophytes: some growing vertically and some horizontally (*ibid.*). As there is no inflammatory aspect to DISH (Marzo-Ortega, *et al.* 2002), differences in joint involvement can also be distinguished by their inflammatory (AS) or their non-inflammatory (DISH) nature (Kozanoglu, *et al.* 2002). However, this conjunction of diseases has been found to be rare; only ten cases were reported prior to 1996 (Moreno, *et al.* 1996). Osteoarthritis can also co-exist with DISH and has been found to be more severe and affect joints not normally associated with osteoarthritic changes (Mader 2002). They can be differentiated by the presence of enthesopathies in DISH (Mazières and Rovensky 2000).

5.3.2 Palaeopathological Diagnostic Criteria

Unlike the SpA, DISH has been diagnosed in numerous skeletal remains. Roberts and Cox (2003) list 211 cases of DISH out of a total of 7854 skeletons. The disease has been found in many periods ranging from an example in a Neanderthal skeleton from

Iraq (Roberts and Manchester 2005) to post-medieval cases from St. Martin's, Birmingham (Brickley, *et al.* 2006). However, the disease does appear to have become more frequent over time, which some authors (Roberts and Cox 2003) have suggested may be linked to increased sedentism. Another trend, not yet understood, is the increased prevalence of the disease in monastic cemeteries compared with lay cemeteries from the same time period and geographic location (Roberts and Manchester 2005; Rogers and Waldron 1995, 2001). Whether this represents dietary differences (Harvey 1993; Rogers and Waldron 2001); increased longevity in the monastic population (de Gouw, *et al.* 1995; Leveringhaus 2003); or other lifestyle differences between the monastic and local population, remains to be ascertained.

The diagnostic criteria for palaeopathologists studying DISH are set out in Table 5.9. These criteria have clearly been directly adapted from the clinical criteria for the diagnosis of DISH, but it is presumably easier to diagnose DISH in skeletal remains, because of the lack of soft tissue surrounding the bone; *i.e.* it may not be necessary to find four vertebrae ankylosed by ossification of the anterior longitudinal ligament in cases which also have florid enthesopathy formation. It should also be noted that some authors (Resnick and Niwayama 1995b; Rogers, *et al.* 1997) even hypothesise that the extra-spinal new bone formation may be the first changes to occur in individuals with DISH. Such considerations are important when creating clear and useful criteria for the diagnosis of this disease.

Table 5.9 Palaeopathological diagnostic criteria for the diagnosis of DISH.

Criteria	Comment
Fusion of a minimum of four vertebrae (Aufderheide and Rodríguez-Martín 1998; Roberts and Manchester 2005; Rogers and Waldron 1995)	Fusing bone should arise from the antero-lateral and right aspect of the vertebral bodies (Aufderheide and Rodríguez-Martín 1998) (or, presumably the left aspect if there is cause to suspect *situs inversus*).
Intervertebral disc space is not affected (Aufderheide and Rodríguez-Martín 1998; Rogers and Waldron 1995)	
Vertebral end plates are not affected (Aufderheide and Rodríguez-Martín 1998)	

Criteria	Comment
The anterior longitudinal spinal ligament is ossified (Aufderheide and Rodríguez-Martín 1998; Rogers and Waldron 1995)	The ossified ligament gives a "dripping candle wax" appearance to the spine and is dense and homogenous (Aufderheide and Rodríguez-Martín 1998)
The apophyseal joints are not affected (Aufderheide and Rodríguez-Martín 1998)	
Process usually begins in the mid-thoracic spine (Aufderheide and Rodríguez-Martín 1998)	
Extra-spinal entheses are commonly affected (Aufderheide and Rodríguez-Martín 1998; Rogers and Waldron 1995)	The entheses are ossified leading to enthesopathy formation: particularly common in the lower extremity (Aufderheide and Rodríguez-Martín 1998)
Sacroiliac joint involvement can occur (Aufderheide and Rodríguez-Martín 1998)	No intra-articular bony ankylosis (Aufderheide and Rodríguez-Martín 1998)

Differential diagnoses of DISH that are generally considered in the palaeopathological literature are: AS (Aufderheide and Rodríguez-Martín 1998; Mann and Murphy 1990; Roberts and Manchester 2005; Rogers and Waldron 1995), acromegaly (Rogers, *et al.* 1997) and fluorosis (Littleton 1999). The same criteria are used as in clinical literature to differentiate between the skeletal manifestations of these arthropathies. The primary difference is that only DISH has the "dripping wax-like" anterior longitudinal ligament calcification (Grimaldo, *et al.* 1995) and no joint surface changes.

5.4 Fluorosis

Fluorosis is a disease caused by the dietary intake or inhalation of excessive quantities of fluoride (Cao, *et al.* 2003; Grimaldo, *et al.* 1995; Reddy, *et al.* 1998; Resnick 1995c; Sticht 1998; WHO 2000, 2003a, b). Fluoride is the negative ion of fluorine, which is a highly reactive halogen gas (Sticht 1998). Fluoride compounds are widely found in the natural environment, in such minerals as fluor-spar (CaF2), and apatite [Ca5(PO4)3(OH, Cl, F)] (Sticht 1998) which is often impure with four to six percent of the phosphate groups (PO4) being replaced by carbonate (CO3), especially at the edges and the highly vascularised zones (Currey 2002)]. Consequently, naturally high-levels of fluoride in water occur in areas where water has flushed the fluoride from the rocks, *e.g.* at the foot of high mountains and in regions previously covered

by the sea (WHO 2003b). These zones stretch from Syria, through Jordan and south to Kenya, from Turkey east towards northern Thailand and China, as well as regions in the Americas and Japan (WHO 2003a). Food products can also be a source of fluoride (Cao, *et al.* 2003; Sticht 1998; WHO 2000, 2003b). Almost all foodstuffs contain some fluoride derived mainly from water, soil or the air (WHO 2003b). High levels are found in curly kale, endive, taro, yams, cassava, fish, and tea (WHO 2000, 2003b). Cooking food in fluoride-rich water or curing it over a fluoride-rich fuel increases the levels of fluoride consumed by an individual (Cao, *et al.* 2003). Boiling water also increases its fluoride content (Grimaldo, *et al.* 1995).

Fluoride is not only present in water, but also in the air (Aufderheide and Rodríguez-Martín 1998; Cao, *et al.* 2003; Resnick 1995c; Sticht 1998; WHO 2000). Naturally occurring fluoride in the air occurs from geological deposits and is thought to be concentrated at *circa* 0.5ng/m^3 of air (WHO 2003b). Recent industrial emissions have raised this background level to *circa* 3ng/ m^3 (*ibid.*), but some areas have higher localised concentrations. Localised concentrations of airborne fluoride dust occurs in proximity to aluminium, fertiliser, glass, ceramic, and brick industries and can be inhaled by livestock, thus increasing fluoride content of meat [but probably not milk, because human breast milk, even in areas of endemic fluorosis, has been found to be low in fluoride (WHO 2003a)] and humans (Sticht 1998). In most cases airborne fluoride dust does not pose a risk to health. However, in areas of China where high-fluoride coal is used for cooking (as well as drying and curing food) in poorly ventilated indoor environments these levels [16-46 μg/m^3 (WHO 2003a)] can cause skeletal fluorosis (Cao, *et al.* 2003; WHO 2003b).

It is calculated that skeletal fluorosis affects millions of people predominantly in Africa and Asia (Reddy, *et al.* 1998; WHO 2003a). It is endemic in some regions of the world. For example, in two villages in a south-western province of China, 80 percent of the villagers suffer from skeletal fluorosis, caused by cooking over fluoride rich fuel. Ingested fluoride (from water, food or the air) is rapidly absorbed through the gut into the body fluids, at which point *circa* 50 percent is excreted in the urine and through sweat (Resnick 1995c; Sticht 1998; WHO 2000). The remaining fluoride is deposited in the skeleton (Resnick 1995c; WHO 2000) in the form of fluoro-apatite

[$Ca_5(PO_4)_3(F)$], particularly in the trabecular bone (Littleton 1999) and probably in other highly vascularised areas (Currey 2002). In part, bone is composed of hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$], which is often impure, with four to six percent of the phosphate groups (PO_4) being replaced by carbonate (CO_3), particularly at the margins of the bone and these highly vascularised areas (Currey 2002). It is, as yet, unknown (Cao, *et al.* 2003) what concentrations of fluoride in the diet are required to cause skeletal fluorosis, although, concentrations of fluoride over 3mg/l in drinking water have been known to cause bone changes (WHO 2003a). Dietary deficiencies and the dietary intake of other minerals can respectively decrease or increase the amount of fluoride required to cause bone changes (Reddy, *et al.* 1998; WHO 2003a). The symptoms, diagnostic criteria, and differential diagnoses will be considered in the following section.

5.4.1 Clinical Diagnostic Criteria and Differential Diagnosis

The physical signs of skeletal fluorosis are the inability to completely flex the arms, difficulties in squatting, general restricted movement, kyphosis, and sometimes paralysis (Cao, *et al.* 2003). Radiographic evidence of skeletal changes is most obvious in the spine, pelvis, and ribs (Resnick 1995c). These changes can be found in both adults and children (Krishnamachari 1086). Osteosclerosis, osteopenia and osteomalacia are often the first findings, especially in subadults (Resnick 1995c). Vertebral osteophytes can impinge on the spinal canal space and the intervertebral foramina (Savas, *et al.* 2001). Enthesopathies can be widespread. Entheses affected can include those at the inferior margins of the ribs leading to restricted chest movement, while calcification of the paraspinal and intraspinal ligaments can further reduce mobility (Resnick 1995c).

In the appendicular skeleton osteosclerotic changes are less common, but osteopenia is an early finding (Resnick 1995c). Fluoride stimulates bone metabolism causing an increase in osteoblast activity leading to new bone formation (Savas, *et al.* 2001). The periosteal surface of the bone can become thickened, ligaments can become calcified, and calcification can occur in the muscles. In severe cases, the periosteal bone

formation can take over, leading to long bones becoming "cloaked" in periosteal bone. This is associated with cortical thickening, the reduction in size of the medullary space, endosteal bone formation, enthesopathies, and periarticular osteophytes (Resnick 1995c).

In areas of endemic skeletal fluorosis, it has been found that elderly individuals have more indicators of skeletal fluorosis than younger individuals (*i.e.* there was a positive correlation between severity and prolonged exposure, which is similar to DISH and bone formers) (Cao, *et al.* 2003). It is unlikely that this is caused by changes in exposure, because skeletal fluorosis can be remodelled away if fluoride levels drop. This takes around eight years (Resnick 1995c).

Although each individual radiographic finding in fluorosis is similar to at least one other disease, taken as a whole radiographic signs of fluorosis differ from any other disease (Resnick 1995c). See Table 5.10 for a list of radiographic features and their differential diagnoses.

Table 5.10 Radiographic features of fluorosis with their differential diagnoses adapted from (Resnick 1995c).

Radiographic Feature	Differential Diagnoses
Osteosclerosis	Skeletal metastasis, myelofibrosis, mastocytosis, some hemoglobinopathies, renal osteodystrophy, Paget's disease, congenital disorders.
Vertebral osteophytosis and similar outgrowths	Spondylosis deformans, DISH, AS, PsA, EA, acromegaly, neuropathic osteoarthropathy, alcaptonuria.
New bone formation at entheses	DISH, hypoparathyroidism, X-linked hypophosphatemic osteomalacia, some plasma cell dyscrasias
Periostitis	Hypertrophic osteoarthropathy, pachydermoperiostitis, thyroid acropathy

5.4.2 Palaeopathological Diagnostic Criteria

Diagnosis of skeletal fluorosis in palaeopathology should be straightforward due to the extreme nature of the bone formation involved (Aufderheide and Rodríguez-Martín 1998). Not only does the shape of the bones differ from normal, but their density is also increased (Aufderheide and Rodríguez-Martín 1998; Resnick, *et al.* 1975). Fluoride content of bones and teeth can be used to confirm the diagnosis, but levels should be compared to the fluoride content of the burial surroundings and other unaffected skeletons, because of the problem of fluoride diagenesis (Aufderheide and Rodríguez-Martín 1998; Littleton 1999).

Littleton (1999) described a large sample (255 skeletons) from Bahrain's Hellenistic period (*ca.* 250 BC-AD 250). Four percent of these individuals, predominantly males in the older age categories (50+), had lesions characteristic of skeletal fluorosis or DISH (*ibid.*). Differentiating between the two conditions, according to Littleton (*ibid.*), requires the presence of complete or near complete skeletons. However, it should be noted that neither osteosclerosis nor periosteal bone formation is a characteristic feature of DISH. These factors, combined with the presence of high local fluoride levels, should be taken into account when diagnosing skeletal lesions of this nature. Due to the local fluoride content of water, the dietary reliance on fish (a foodstuff with a high fluoride content), the heat (a known predisposing factor, due to the increased reliance on water), and the characteristic skeletal lesions, these skeletons were diagnosed as having skeletal fluorosis (Littleton 1999). Differential diagnoses to consider in palaeopathology are the same as those in clinical literature (see Table 5.10).

It is worth noting that one proposed aetiology for DISH is exposure to high-levels of fluoride (Resnick and Niwayama 1995b). Although this has been discredited, it is possible that a combination of factors, including fluoride exposure, could cause (or increase susceptibility to) this disease. For this reason it would be interesting to plot the occurrence of DISH in relation to natural fluoride content of water and fish consumption. Another bone forming disease, ossification of the posterior longitudinal

ligament, is found in populations with high dietary fish consumption (Inamasu, *et al.* 2006).

5.4.3 The Palaeopathological Implications

It is likely that further cases of skeletal fluorosis will be discovered, particularly in countries such as China and India. In Britain, no cases are likely, but in parts of some American states, for example New Mexico and Texas (Ayers and Westcot 1984), it might be found. These findings will provide information on water sources, and cooking techniques.

5.5 Lyme Disease

Lyme disease is named after a town in Connecticut, USA, where it was first diagnosed in 1975 (Habicht, *et al.* 1990). In North America it is caused by the spirochete bacterium *Borrelia burgdorferi*, identified in 1981. This gram-negative bacterium is flexible and spiral shaped with internal flagella (Johnson 1996). In Europe two species: *B. afzelii* and *B. garinii* are also involved in pathogenesis (and *B. valaisiana* in Britain; Smith *et al.* 2000). These are transmitted to humans by tick bites. Other spirochetes pathogenic to humans are: Treponemes and Leptospires (Malawista 2001). In all of these diseases, the infection runs an intermittent course, with remissions and exacerbations (Chary-Valckenaere, *et al.* 1995) and not all cases become chronic. It is not understood how the spirochete enters the bloodstream. However, its intermittent course and remissions are explained by the ability of this spirochete to undergo several antigenic variations, by which the organisms effectively disappear in response to the immune response launched by the body (Johnson 1996).

Two species of tick transmit Lyme disease: the tick *Ixodes dammini* in North America, and *I. Ricinus* in Europe. Deer are the most common carriers of these ticks. Other species of tick are also thought to be vectors, but there is no laboratory support for this (Malawista 2001). The primary source of the infection is bites from the nymph, although adult female ticks can also transmit the disease (Johnson 1996). The

spirochetes are found in the mid-gut of the tick and require feeding of the tick on the host of between 12 to 24 hours (Johnson 1996).

In rare cases, human-to-human transmission may be possible, both sexually and from mother to baby (Harvey and Salvato 2003). The differences in species of spirochete are thought to relate to differences in disease manifestation. In North America there are a higher proportion of arthritic and musculoskeletal symptoms than in Europe, whilst in Europe skin manifestations are associated with *B. afzelii* and neurological complications with *B. garinii* (Smith, *et al.* 2000). In Britain few cases are reported, perhaps because *B. valaisiana* causes few pathological changes (*ibid.*).

All age groups, sexes and mammalian pets (mammals in general, and some species of bird, which may have spread the disease geographically) are at risk, if living in an endemic area (Habicht, *et al.* 1990). However, the majority of cases occur in children under 15 years of age and in middle-aged adults, probably because of activities performed in close proximity to infected vectors (Malawista 2001). In temperate climates onset of the disease is generally between May and November, and peaks between June and July (*ibid.*). In the USA more than 10 000 cases are reported each year; despite this, it is estimated that 1 in 5 cases is not reported (*ibid.*). The frequency of cases reported between 1992 and 2000 in the UK was 0.32 in 100,000, in France 16 in 100,000, in Sweden 80 in 100,000 [but the number of cases peaked in the summers of 1992 and 1993, when the disease became reportable (Smith, *et al.* 2000)], and in Slovakia 120 in 100,000 (*ibid.*).

5.5.1 Clinical Diagnostic Criteria and Differential Diagnosis

The disease often begins with erythema migrans; a red papule at the centre of a red "bull's eye" like rash, spreading out from the initial bite (Chary-Valckenaere, *et al.* 1995). The secondary stage (this disease is often divided into stages, which can overlap) is characterised by multiple skin lesions, influenza-like symptoms, headache and musculoskeletal pain (Malawista 2001). Cardiac, including myocarditis and atrioventricular block, or neurological manifestations (which can include neuropathic

arthropathy (Houtman and Tazelaar 1999), *e.g.* meningitis and facial palsy, can occur, but may be delayed by a period of weeks or months. Other delayed manifestations include intermittent arthritis (which can lead to chronic arthritis), central nervous system involvement, or *acrodermatitis chronica atrophicans*. Not all patients develop all manifestations, or undergo all stages (Tables 5.11, 5.12).

Clinical diagnostic criteria involve recognition of the symptoms described above. Laboratory diagnosis is rarely of assistance because of the difficulty of culturing the bacillus and of finding it in specimens of synovial (or other) tissues (Chary-Valckenaere, *et al.* 1995). Other techniques, such as serological testing and Western blotting can be used but false positives do occur (*ibid.*).

Table 5.11 Three stages of Lyme disease.

Stages	Symptoms and Signs	Occurrence and additional comments
First stage	Erythema chronicum migrans: red papule at site of bite, with a red bull's-eye shaped rash spreading out from this site.	Do not always occur.
	Fatigue, fever, chills, headache (episodic, and excruciating), and backache.	Do not always occur.
	Secondary rashes which lack the central red papule.	Occur in 25-50 percent of patients.
Second stage (does not always occur)	Neurological complications (including meningitis, inflamed nerve roots in the neck, Bell's palsy).	15 percent of patients
	Migratory musculoskeletal pain	
	Cardiac difficulties (irregular electrical impulses to the heart (atrioventricular block), along with palpitations, dizziness, and or shortness of breath	5 percent of patients
Third stage	Musculoskeletal manifestations, which are similar to rheumatoid arthritis. This primarily affects the knees. Other large joints can also be affected, *e.g.* the hips and shoulders. Occurs in bouts of a few days or a few weeks.	Occur in *circa* 60 percent of untreated cases of Lyme disease

Table 5.12 Frequency of symptoms and signs in England. Adapted from Smith *et al.* (2000, p. 406).

Symptom/sign	1986-1992	1993-1996	1997-98	Total
Arthritis	7 %	2 %	3 %	4 %
Other musculo-skeletal symptoms	26 %	13 %	15 %	17 %
Erythema migrans	28 %	41 %	49 %	41 %
Skin involvement	35 %	53 %	61 %	51 %
Neuroborreliosis	21 %	12 %	13 %	15 %
Other neurological symptoms	20 %	7 %	6 %	10 %
Cardiac involvement	0.9 %	0.4 %	0.6 %	0.6 %
Total number of cases	227	235	334	796

Typically the arthritic involvement is not chronic and takes the form of inflammation, myalgia, arthralgia or periarticular pain (Malawista 2001). Chary-Valckenaere *et al.* (1995) define periarticular pain to include entheseal pain and enthesitis and digital swelling can also occur, but this does not involve ossification of entheses. It can involve any joint, normally as monoarthritis (*ibid.*), but in approximately 80 percent of cases affects the knee (Lawson and Steere 1985). In approximately ten percent of patients involvement can become chronic. This is typified by inflammatory joint disease changes (*ibid.*): pannus formation and erosion of cartilage leading to eburnation, most commonly affecting the large joints (Malawista 2001). This cartilage loss can be accompanied by juxta-articular osteoporosis and cortical or marginal bone erosions (Lawson and Steere 1985). Less commonly the changes are more typical of degenerative joint disease, with cartilage loss, subarticular sclerosis and osteophyte growth, but without erosions or osteoporosis (*ibid.*). Joint dislocation and periostitis (particularly located close to lesions of *acrodermatitis chronica atrophicans*) have been reported (Chary-Valckenaere, *et al.* 1995). However, the chronic stage is thought to last for a maximum of four years, even without antibiotic treatment, and the inflammatory process is resolved (Malawista 2001).

Other bony changes have been described. At the bony subcutaneous site of *acrodermatis chronica atrophicans*, cortical thickening has been observed (Houtman and Tazelaar 1999). Neuropathic arthropathy has also been described and is thought to manifest as subluxation particularly of the smaller joints of the lower extremity

(*ibid.*). In those cases described by Houtman and Tazelaar, radiographs taken three years later show that the periostitis and subluxations were still manifest, despite antibiotic therapy. Typical radiographic features include thickening and calcification of tendons surrounding affected joints, but enthesopathy formation seems rare (Lawson and Steere 1985).

5.5.2 Palaeopathological Diagnostic Criteria

The earliest known cases of Lyme disease occurred in 1962 on Cape Cod, USA and 1975 in Lyme, Connecticut, USA, but DNA analysis of ticks collected in the 1940s from Long Island, USA and from two mice collected on Cape Cod, USA in 1894 indicate that the spirochete has existed in the USA for over a century (Malawista 2001). Descriptions of symptoms probably associated with the disease have also been found in medical literature from Europe prior to the 1960s (Leff 1993). An erythema migrans rash was described (and named) in 1909 in Stockholm, Sweden, by Arvid Afzelius. This rash was similarly described in France in 1922 and in Germany in 1934 and the therapeutic effect of treatment with the antibiotic penicillin was also described in 1951 (*ibid.*). There are reports of a chronic arthritic condition called "fillun" in Gaelic occurring on the Isle of Jura (heavily populated with deer, an important host of the ticks which carry Lyme disease) in the 18th century and said to have developed after a worm burrowed into the skin (Summerton 1995). Similarly, there are accounts of links existing in folk beliefs of the Cherokee Native Americans between arthritis and deer (Hudson, *et al.* 1975). Whether these accounts relate to Lyme disease is unknown but, if they do, then they indicate a long history of Lyme disease in parts of Europe and North America.

It has also been hypothesised that Lyme disease provides partial immunity to diseases caused by the spirochete *Treponema pallidum* (*e.g.* yaws and syphilis) (Lewis 1994). Skeletons from the north shore of Lake Pontchartrain, Louisiana (USA) of the Tchefuncte Indians (500 BC to 300 AD) demonstrated mild signs of chronic treponemal infection and a juvenile demonstrated signs of juvenile rheumatoid

arthritis (the signs of which could also be caused by Lyme disease) indicating a possible association between the two spirochetal diseases.

5.5.3 The Palaeopathological Implications

Diagnostic criteria specific for Lyme disease cannot be created because of the lack of skeletal involvement in the majority of cases and the generalised arthropathy that occurs. However, in skeletons with preserved soft tissue it may be possible to recover evidence of Lyme disease. This would be of value, considering the lack of knowledge that currently exists concerning its past, which may be of significant for predicting its future.

5.6 Ochronotic Arthropathy

Ochronotic arthropathy is an arthropathy caused by the deposition of a brown-black pigment in the joint cartilage, in both the axial and appendicular skeleton, of some individuals with alcaptonuria (Laskar and Sargison 1970). Alcaptonuria is an inherited autosomal recessive disorder, involving the mutation of the HGO gene on chromosome 3q (Keller, *et al.* 2005), caused by the lack of homogentisic acid oxidase, present in the normal liver, and also called homogentisate oxygenase (Laskar and Sargison 1970), or homogentisic acid polyphenol oxidase (Zannoni, *et al.* 1969). This enzyme is crucial for the breakdown of tyrosine and phenylalanine (amino acids which are the fundamental components of proteins), which cannot otherwise be metabolised (Laskar and Sargison 1970). Homogentisic acid is accumulated, particularly in the connective tissues, and its oxidisation products are polymerised into a dark polymer possibly through the mediation of benzoquinoneacetic acid (Zannoni, *et al.* 1969). This polymer is then deposited in the same tissues leading to their degeneration (Laskar and Sargison 1970). Homogentisic acid can be excreted through the renal tubular system, which is particularly efficient during youth, although can deteriorate with time (Hamdi, *et al.* 1999). This is probably why ochronosis des not present until after the age of forty, but cases in children have been documented (*ibid.*).

The prevalence of alcaptonuria is lower than 1 in 250,000 (Keller, *et al.* 2005: Mannoni, *et al.* 2005). Ochronotic arthropathy is even rarer, with the incidence placed between 1 in 43 million and 1 in 10 million. Laskar and Sargison (1970) propose that this underestimates the real incidence, which they estimate as being 1 in 500,000 (*i.e.* 50 percent of individuals with alcaptonuria develop ochronotic arthropathy) (*ibid.*). Men are affected with ochronosis twice as often as women (*ibid.*). However, it has been suggested that this might relate to social factors, *e.g.* the examination of urine prior to military service (Resnick 1988a). Higher prevalence rates exist in some populations, *e.g.* the Dominican Republic and a small region in Slovakia (Mannoni, *et al.* 2005) and are thought to relate to genetic isolation and a high mutation rate (Srsen, *et al.* 2002).

5.6.1 Clinical Diagnostic Criteria and Differential Diagnosis

Ochronotic arthropathy is diagnosed by the combination of arthritic changes and alcaptonuria [diagnosed by urine high-performance chromatography for homogentisic acid (Jebaraj and Rao 2006)]. The arthritic changes are characterised by a paucity of osteophyte formation (Borman, *et al.* 2002; Keller, *et al.* 2005), and the blackening of both fibrocartilage and hyaline cartilage (Resnick 1988a). Tissues affected include hyaline cartilage, tendon, ligaments and muscles and their involvement is characterised by weakness, brittleness, cracking and rupture (Keller, *et al.* 2005). The mechanism of these changes is not yet fully understood, but hypotheses range from homogentisic acid acting as a chemical irritant or binding to the connective tissues, thereby altering their structure and mechanical properties (*ibid.*). The degenerative process itself leads to further inflammation of the joints, exacerbating the degenerative process (*ibid.*).

The most characteristic finding in the spine is disc calcification with the nucleus pulposus the last part of the disc to become calcified (Keller, *et al.* 2005; Laskar and Sargison 1970). Narrowing of disc space can lead to eburnation of neighbouring vertebral bodies (Resnick 1988a). Osteophytes and bony bridge formation are also frequently seen at the vertebral margins (Keller, *et al.* 2005; Laskar and Sargison

1970). Other typical changes are sclerosis or osteoporosis of vertebral bodies which can be involved in compression fractures (Laskar and Sargison 1970). Changes to the curvature of the spine, caused by loss of joint space, vertebral ossification and compression fractures are seen as loss of lumbar lordosis and exaggeration of thoracic kyphosis (Keller, *et al.* 2005). This can cause loss of height (Resnick 1988a). The cervical spine is usually unaffected by loss of movement (Laskar and Sargison 1970). The changes seen, such as restricted chest expansion, spinal deformation and involvement of the sacroiliac joint (Resnick 1988a), have been likened to those in spondyloarthropathy and the term "ochronotic spondyloarthropathy" has been used (Balaban, *et al.* 2005). However, the typical spinal ligament ossification of the seronegative spondyloarthropathies does not occur and the sacroiliac joint involvement does not involve ankylosis, just joint space narrowing, sclerosis and osteophytosis. Consequently, the inclusion of this disease in this group is thought to be erroneous (Laskar and Sargison 1970).

The large joints, *e.g.* the hip and knee are the most commonly affected (and can be affected symmetrically), with evidence of cartilage degeneration, joint space narrowing, sclerosis and minimal osteophyte formation (Keller, *et al.* 2005). Eburnation of the synovial joint can also occur (Resnick 1988a). Other joints, such as the shoulders (Borman, *et al.* 2002), and elbow (Resnick 1988a), as well as the distal interphalangeal joints, can be affected by restricted movement (Sahin, *et al.* 2001). However, typically the small joints are not affected (Laskar and Sargison 1970). Pelvic changes can also be found, both at the sacroiliac joint and the pubic symphysis, and are characterised as joint space loss, calcification and rarely bony bridging (Resnick 1988a). The hyaline cartilage degenerates as it becomes brittle, leading to fibrillation and subsequent exposure of deeper layers of cartilage and eventually bone (*ibid.*). The bony joint surface can then become eburnated or sclerotic and loose fragments of cartilage can become embedded in synovial membrane or marrow (*ibid.*) and joints can become fixed (Laskar and Sargison 1970).

The peri-articular soft tissues lose elasticity and develop poor mechanical resistance, caused by pigment deposition (Borman, *et al.* 2002). Other researchers (Jebaraj and Rao 2006) have demonstrated loss of fibrillary pattern in the tendon, along with increased thickness. In cases of tendon or ligament ruptures, which can be

spontaneous (Kumar and Rajesekaran 2003) deposition of the black pigment has been observed on both sides of the rupture (Ando, *et al.* 2004). In the case discussed by Ando and colleagues (*ibid.*) there were no normal collagen bundles where deposition of pigment was found, in this case, at the Achilles tendon insertion and a region (ruptured) close to that. Common sites of ruptures are the Achilles tendon and the patellar tendon (Kumar and Rajesekaran 2003), and in the former the ruptures commonly occur at the insertion (Ando, *et al.* 2004). Enthesopathies, seen as bone spurs or "whiskers", have been reported in the pelvis (Resnick and Niwayama 1983), the Achilles tendon (Jebaraj and Rao 2006), calcaneus, and trochanters (Niepel and Sitaj 1979). Calcification can also affect the attachment of the joint capsule (Laskar and Sargison 1970). Cysts can also develop at entheses of ligaments and tendons, (*ibid.*). Other extra-skeletal calcific deposits can also occur such as renal calculi, prostatic calculi, and calcification of the costal cartilages (which can lead to rigidity of the thorax) (*ibid.*).

Differential diagnoses of ochronotic arthropathy are those diseases that affect the spine or are involved in degenerative changes of the joints. Examples of these diseases are: degenerative joint disease (osteoarthritis), AS, rheumatoid arthritis, calcium pyrophosphate deposition disease (CPPD), hyperparathryoidism, haemochromatosis, amyloidosis, or DISH (Borman, *et al.* 2002). However, none of these involve the black deposits or disc calcification associated with ochronotic arthropathy. Calcification of the menisci of the knee can also aid differential diagnosis (Laskar and Sargison 1970). The vertebral body bridging in ochronotic arthropathy is broad and "band-like" (Resnick 1988a), in contrast to the syndesmophytes seen in the SpA (see Section 5.2.1). Severe degenerative disease with symmetric joint space loss in the synovial joints (particularly if osteophytes are small or infrequent) raises the possibility of ochronotic arthropathy, as this rarely occurs in degenerative joint disease (Resnick 1988a). Severe degenerative changes in the shoulder are also rare, unless caused by trauma (*ibid.*).

5.6.2 Palaeopathological Diagnostic Criteria

In dry bone, cases of ochronosis cannot be suspected because the characteristic black pigment deposition cannot be identified (Ortner 2003a). On dry bone osteophytic

bridging, with loss of normal spinal curvatures, along with osteoarthritis (with minimal osteophyte presence) of the large joints, would be the only diagnostic criteria in dry bones, unless molecular analyses were used. However, cases of ochronosis in mummified remains have been identified (Aufderheide and Rodríguez-Martín 1998; Ortner 2003a). Radiographs identified extensive calcification of intervertebral discs and articular narrowing in the hips and knees in an Egyptian mummy from 1500BC (Stenn, *et al.* 1977). A biopsy of the right hip demonstrated parallel black regions in its cartilage. This black pigment was analysed and appeared identical to homogentisic-acid-derived polymer found in individuals with ochronotic arthropathy.

5.6.3 The Palaeopathological Implications

Ochronosis is rare in Great Britain, but there are other European areas where the disease is more common, such as Slovakia, where the incidence is 1 in 19,000 (Srsen, *et al.* 2002). Although there is no simple explanation, it is thought that genetic isolation (*ibid.*), along with possible chemical or physical agents lead to increased mutation of this gene (Zatkova, *et al.* 2000). Whether such clustering of ochronosis existed in other isolated communities in the past, but which have now died out, is unknown. Future research into this condition could be possible in mummified remains.

Diagnostic criteria for this disease are: the presence of a dark pigment in connective tissues, disc space loss in the spine and synovial joints, ossification of the vertebral discs, severe degenerative joint disease of the large joints (hip, knee and shoulder) with minimal osteophytosis, and enthesopathies.

5.7 Acromegaly

Acromegaly is caused by the hyper-secretion of human growth hormone after skeletal maturity caused by adenomas (which are normally benign) of the pituitary gland (Colao, *et al.* 2004). It is characterised by: enlargement of facial features and the hands and feet (Resnick 1988b). Changes in shoe or glove size are typical (Lioté and

Orcel 2000). Features of acromegaly were first described in a female autopsy cadaver in 1864 and many similar cases were described between then and the start of the 20th century, but it was not until 1909 that the link between skeletal hypertrophy and hyper-secretion of growth hormone was made by Harvey Cushing (Colao, *et al.* 2004). Acromegaly only affects the skeletally mature, typically occurring in the 3rd and 4th decades of life (Resnick 1988b). Hyper-secretion of growth hormone prior to epiphyseal fusion leads to gigantism or the proportional increase in size (length and width) of bone (Berkow 1982). Gigantism will not be discussed in this chapter, because it is not associated with enthesopathies (Resnick 1988b).

Acromegaly is not a common disease. Its annual incidence is approximately 3.5 per 1,000,000 with a prevalence estimated at between 40 and 90 cases per 1,000,000 (Colao, *et al.* 2004). In the Newcastle area of Northeast England, there are an estimated 53 individuals per 1,000,000 with acromegaly (Katznelson 2005). There is an equal frequency of the disease between males and females (Resnick 1988b) and more than half have arthritic conditions (Lioté and Orcel 2000).

Human growth hormone secretion is regulated by the hypothalamus (Katznelson 2005). Growth hormone stimulates production of insulin-like growth factor I (IGH-1) from the liver and other organs and these two hormones themselves regulate growth hormone secretion at the hypothalamus by a system of negative feedback (*ibid.*). In the normal pituitary gland, secretion of growth hormone occurs from somatotroph cells and the most common cause of acromegaly in 95 percent of cases is pituitary somatotroph adenoma (*ibid*), which is typically benign (Resnick 1988b). Extra-pituitary or hypothalamic tumours can also cause acromegaly, but these are rare (Ganong 2001).

5.7.1 Clinical Diagnostic Criteria and Differential Diagnosis

The "classical" features of an advanced acromegalic patient are facial changes, such as frontal bossing, protruding jaw and widely spaced teeth, and in the postcranial skeleton typical features are enlarged hands and feet (Katznelson 2005). Clinical features are listed in Table 5.13. Diagnosis of acromegaly is normally achieved

through biochemical analysis of growth hormone levels in the body and MRI scans can be used to determine the presence of a pituitary adenoma (*ibid*).

Table 5.13 Clinical features of acromegaly, adapted from Lioté and Orcel (2000, p. 103).

Cause of changes	Changes seen	Examples of changes
Direct effect of tumour	Headache	
	Visual problems	Caused by pressure from the enlarged pituitary gland (Resnick 1988b).
	Hyperprolactinaemia	
	Hypopituitarism cavernous sinus syndrome	
Systemic effects of hypersecretion of human growth hormone	Soft tissue changes	Hyperplasia of soft tissues; increased sweating;
	Cardiovascular disorders (cause of death in approximately 60 percent of patients	Arrhythmia; hypertension; cardiac valve disease; cardiac hypertrophy; but congestive heart failure is rare (Colao, *et al.* 2004).
	Metabolic changes	Diabetes mellitus; insulin resistance; reduced total cholesterol; increase in triglycerides
	Respiratory changes (cause of death in approximately 25 percent of cases	Upper airway obstruction; sleep apnoea
	Skeletal changes	Increased articular cartilage thickness; osteophyte formation; enthesopathy formation; carpal tunnel syndrome; osteopenia
	Other changes	Hyperparathyroidism; hypercalciuria; malignant growths (malignancy is the cause of death in approximately 15 percent of cases

Non-musculoskeletal involvement is of considerable importance in acromegaly, but only a brief summary of involvement will be discussed here. Cardiac involvement is common, and normally begins with cardiac hypertrophy with increased systolic output, which in the second phase becomes insufficient on exercise with increased evidence of cardiac hypertrophy and in the final stage heart failure and dilative cardio-

myopathy occur (Colao, *et al.* 2004). The respiratory system can also be affected. Bone and cartilage changes (described below) can cause stiffening of the rib cage. while soft tissue changes can lead to impaired airflow, and organ changes can lead to emphysema. Metabolic complications include diabetes mellitus and alteration in lipid metabolism, which may have a role to play in cardiac involvement (*ibid*).

Musculoskeletal symptoms are common and range from axial and appendicular articular manifestations and enthesopathies (*ibid*). Articular manifestations occur in over half of all patients (Lioté and Orcel 2000) and can progress, despite growth hormone level reduction, if significant cartilage damage has occurred (Dons *et al.* 1988). The duration of acromegaly is not correlated with the severity of arthropathy (Colao, *et al.* 2004). The more common bony manifestations of acromegaly are: periosteal new bone formation and reactivation of endochondral bone formation at bone cartilage junctions, such as the vertebral disc to bone junction (Resnick 1988b). The most common signs of acromegaly are: skull enlargement especially of the supraorbital ridges, but also osteopenia of the sella turcica, enlargement of the mandible, particularly the mental eminence and mandibular rami, along with deepening of the alveolar sockets, enlargement of the frontal sinuses, broadening and enlargement of hands and feet with increased finger and toe separation, general prominence of tuberosities, soft tissue thickening and enthesopathies (*ibid.*).

Axial manifestations of acromegaly include widening of intervertebral disc spaces, enlargement of the vertebral body, typically antero-posteriorly (Lioté and Orcel 2000), osteophyte formation, ligament enthesis ossification and an increase in both thoracic kyphosis and lumbar lordosis (Colao, *et al.* 2004; Lioté and Orcel 2000; Resnick 1988b). Both increased and decreased mobility of the spine are reported, the former probably caused by an increase in vertebral disc thickness, due to marginal formation of cartilage (Resnick 1988b) and lax paravertebral ligaments, whereas the latter is probably related to vertebral bony bridging of the type associated with DISH (Colao, *et al.* 2004). Radiographically, the changes seen are antero-posterior enlargement of the vertebral body caused by subperiosteal new bone formation on the anterior vertebral body surface, ligament ossification, increased vertebral disc space, osteophyte formation, apophyseal joint hypertrophy; and "scalloping" of the posterior aspect, particularly in the lumbar spine (Lioté and Orcel 2000; Resnick 1988b).

According to Colao and colleagues (2004), the most common regions of the spine to be affected are the sacral, lumbar and cervical spines.

Changes almost pathognomonic of acromegaly are the combination of osteophytes, with widening of the joint space (Resnick 1988b). Common sites of appendicular joint involvement are the knees, hips and shoulder joints (Lioté and Orcel 2000; Resnick 1988b). Resnick (1988b) described changes at other less common sites: the elbows, and joints of the ankles, wrists, hands and feet. These changes are characterised both by cartilage hypertrophy and cartilaginous and osseous degeneration. Cartilage changes in acromegaly are characterised by proliferation of new cartilage associated with increased chondrocyte activity, and this leads to ulceration and fissuring of superficial cartilage layers and progressing to deeper layers. This leads to a cycle of cartilage production and destruction leading to areas calcifying and ossifying and an increase in joint space. However, continuing degenerative changes subsequently lead to characteristic degenerative joint disease manifestations, *i.e.* sclerosis, progressive osteophytosis and joint space narrowing. This does not represent an inflammatory response, but probably relates to the effect of growth hormone on cartilage cell metabolism (Resnick 1988b).

Enthesopathies are common in acromegaly; commonly affected sites are: on the posterior and inferior portions of the calcaneus, on the patella, the trochanters of the femora, tuberosities of the humerus and the inferior surface of the clavicle (Resnick 1988b). Enthesopathies have also been found on the skull, hands, feet and pelvis (Resnick and Niwayama 1983).

Differential diagnoses to consider are degenerative joint disease, pachydermoperiostitis and, in the spine, DISH. All of which can be distinguished from acromegaly by the lack of increased growth hormone production. Degenerative joint disease does not involve the characteristic facial and appendicular changes associated with acromegaly, nor the widening of joint space. Pachydermoperiostitis is a rare autosomal dominant hereditary disorder characterised by digital clubbing, pachydermia (the thickening of the facial skin) and periostosis, and is associated with, among other changes, arthritis (Goyal 2006; Resnick 1988b). It affects children and adolescents and is normally active for between 5 to 20 years, before stabilising (Goyal

2006). Radiographic characteristics of this disease are: subperiosteal new bone formation, typically on the distal tibia, fibula, radius, ulna, metacarpals and phalanges, acro-osteolysis, enlargement of sinuses, cortical thickening, and ossification of ligaments and interosseous membranes (Goyal 2006)ear whether the ligament ossification involves enthesopathies. This can be distinguished from acromegaly by the lack of changes to the sella turcica, lack of phalangeal tuft changes and no enlargement of joint spaces (Resnick 1988b). Spinal changes can appear similar to DISH if ossification has bridged the intervertebral disc space on the anterior border of the vertebral bodies (Colao, *et al.* 2004).

5.7.2 Palaeopathological Diagnostic Criteria

Only a few cases of acromegaly have been published in the palaeopathological literature (Ortner 2003b). Diagnosis of these has been based on the musculoskeletal changes described above. This disease is interesting for palaeopathologists because is can potentially provide insight into the social acceptance of disability in the past.

5.8 Ossifying Diatheses (Bone Formers)

It has been proposed that diseases such as hypertrophic OA, sternocostoclavicular hyperostosis and DISH are not "real" diseases, but are instead ossifying diatheses, *i.e.* the individuals with these conditions have an inherent propensity to form bone (Cammisa, *et al.* 1998; Garber and Silver 1982; Resnick and Niwayama 1995b; Rogers and Waldron 1995, 2001; Sartoris, *et al.* 1986). However, others (Waldron and Rogers 1990) have found that DISH and ossifying diatheses (bone forming) are distinct entities. These bone formers (characterised in the skeleton as a positive association between osteophyte and enthesopathy formation) might have an exaggerated response to repeated trauma (Resnick and Niwayama 1995b; Rogers and Waldron 2001), abnormal stresses (Resnick and Niwayama 1995b), or obesity (Rogers, *et al.* 1997). Obesity probably causes secondary biomechanical stress in that obese people's bones and joints have to withstand the stress of carrying their own

weight. DISH might be at the extreme end of the spectrum of bone forming. but those closer to normality might be the individuals recorded as having MSM.

Bone forming correlates with age: the older an individual is the more likely that he or she has enthesopathies or osteophytes (Rogers, *et al.* 1997). Males also seem to be more prone to these changes than women (*ibid*); this might be because women are prone to osteoporosis and osteopenia due to the lack of oestrogen after the menopause (Dandy and Edwards 1999). The correlation with increased age might also be due to the accumulation of repeated stress over a lifetime.

Recently, MSM have been noted on juvenile skeletons from Bamburgh (Groves, S. pers. comm.). It is currently unclear whether sub-adults or young adults could also be bone formers and that the enthesopathies found on older skeletons originated in childhood or early adulthood. Further research on skeletal biology is required to fully understand what causes bone formation, how this relates to the phenomenon of the bone former and the implications this has for palaeopathology.

5.9 Miscellaneous Diseases

1.1.

5.9.1 Leprosy

Leprosy is a disease caused by the gram positive, acid-fast bacillus *Mycobacterium leprae* (Enna 1982) and is associated with considerable social stigmata, both in the past (Porter 1999b) and present (Remme, *et al.* 2006). Cases of leprosy occur worldwide, but the burden of disease is now limited to Brazil, India, Madagascar, Mozambique, Nepal, and Tanzania (*ibid*). Leprosy is a well-documented disease of the past in texts, such as the liturgical handbook the Sarum Urs, which describes the social and religious exclusion of individuals with leprosy (Porter 1999b), iconography (particularly medieval carvings), architecture (the leprosy hospitals) and the skeletons themselves (Roberts and Manchester 2005). Archaeological skeletal evidence for leprosy in Britain comes predominantly from southern and eastern England, possibly

reflecting archaeological excavation due to building work, along with ideal soil conditions for skeletal preservation (Roberts 2002). It also reflects an increase in leprosy through time from the first known cases in the 4th century AD into the post-medieval period (*ibid*), but the disease has died out by 1798 (Ortner 2003c). One of the primary problems with the palaeopathological study of leprosy is the limited number of individuals with characteristic skeletal involvement. Deformity from nerve damage is estimated to occur in 25 percent of cases (Enna 1982). However, skeletal changes are estimated to occur only in 5 percent of individuals (Resnick and Niwayama 1988), but are not always pathognomonic of the disease (Roberts and Manchester 2005). Leprosy's disease spectrum ranges from the high resistant tuberculoid, through to the low resistant lepramomatous form (Enna 1982). Nerves are affected in all forms of leprosy, but skeletal changes, including enthesopathy formation, are most common in the latter form (Carpintero-Benítez, *et al.* 1996; Ortner 2003c). Carpintero-Benítez and colleagues (1996) hypothesise that the enthesopathies are caused by recurrent local trauma to the entheses causing inflammation. Cartilaginous exostoses have also been reported (Ortner 2003c). Table 5.14 presents some of the skeletal changes and enthesopathy type and location.

5.9.2 Hyperparathyroidism

Enthesopathies have been described in both hyperparathyroidism and hypoparathyroidism (Resnick and Niwayama 1983). The prevalence of the disease was 4.3 per 1,000 in Sweden and is more common in females than males (Melton 1991). Primary hyperparathyroidism is a condition caused by excessive parathyroid hormone secretion by one or more of the parathyroid glands, whereas secondary hyperparathyroidism is caused by an increase in parathyroid hormone due to normal stimulus (Berkow 1982). This latter condition occurs in cases of renal insufficiency and in some intestinal malabsorption syndromes. The disease is characterised by hypercalcaemia, hypophosphataemia and abnormal bone metabolism normally leading to bone mass reduction (*ibid*). According to Resnick and Niwayama (1983) resorption of bone at both tendinous and ligamentous entheses can occur. Typical sites for this are: femoral trochanters, ischial tuberosities, humeral tuberosities, inferior calcaneal surface, inferior distal clavicle and the proximal ulna. Erosion can also

occur on the inferior aspect of the clavicle, at the conoid tubercle and trapezoid line (Schwartz, *et al.* 1977). These authors also observed coracoclavicular ligament enthesopathy. The palaeopathological literature presents some cases of this disease, but diagnosis requires histology to visualise the increased osteoclast activity, seen as subperiosteal porosity and on trabeculae as an uneven surface (Aufderheide and Rodríguez-Martín 1998). In advanced cases the skeletal changes described in the clinical literature have been found in archaeological skeletons (*ibid.*).

5.9.3 Hypoparathyroidism

Idiopathic hyperparathyroidism is rare and caused by an absence or atrophy of the parathyroid glands or by the inability of the organs to respond to the parathyroid homone (Berkow 1982). This can be inherited, occur sporadically, be part of the DiGeorge syndrome or the genetic syndrome of hypoparathyroidism, Addison's disease, and mucocutaneous candidiasis (*ibid.*). Hypoparathyroidism is characterised by hypocalcaemia with neuromuscular symptoms (Lioté and Orcel 2000), and soft tissue ectopic calcifications are also common (Korkmaz 2005). In some cases spinal calcifications akin to AS or DISH have been observed (Korkmaz 2005; Lambert and Becker 1989). These have been described as calcifications of the posterior paraspinal ligaments, apophyseal joint calcification, with preservation of the intervertebral disc space (Korkmaz 2005). Extra-spinal enthesopathies have been described around the pelvis, for example at the ischial tuberosities, and at other sites (*ibid.*). Lambert and Becker (1989) concluded that cases of hypoparathyroidism associated with such bone formation, occurred in patients with an ossifying diathesis in which the underlying parathyroid pathology stimulated the bone growth. However, because of the lack of specific signs for this disease, it has not been found in archaeological skeletal remains, although it has been considered as differential diagnosis (Aufderheide and Rodríguez-Martín 1998).

5.9.4 Hypothyroidism

Unlike hypoparathyroidism, hypothyroidism has been described in the palaeopathological literature (Ortner 2003d). The thyroid hormones are critical for both growth and normal skeletal development as they increase the frequency of the remodelling process by shortening the period of resorption and formation of bone (Lioté and Orcel 2000). Hypothyroidism can be caused by an autoimmune disease and some goitres, and results in a thyroid gland with little to no functionality (Levey 1982). Most clinical texts focus on the symptoms, such as muscle weakness, anaemia and mental disorders, but not the skeletal changes. However, no mention of enthesopathy formation occurs in this disease (Resnick 1988d). The only mention of this sign was found in a list of diseases thought to be associated with enthesopathy formation (Cush and Lipsky 2001).

5.9.5 Behçet's Disease

Behçet's disease is a multisystem inflammatory disorder (affecting multiple organs) of unknown aetiology. The prevalence of this disease is between 1 in 10,000 and 1 in 1,000 (Everekliogl u 2005). In general, males are more severely affected than females (Saylan, *et al.* 1999). The Turkish dermatologist Hulusi Behçet first described it in 1937 as a triad of symptoms: oral and genital ulceration and uveitis (Everekliogl u 2005). It normally manifests itself in the third decade of life (Smith 1982), but can occur in children (termed juvenile Behçet's disease) (Saylan, *et al.* 1999). The disease can affect the mucocutaneous, musculoskeletal, ophthalmological, vascular and central nervous system. Although the disease is generally benign, periods of remission and relapse can extend over several decades, but chronic disease can occur in any organ affected (Everekliogl u 2005). The disease has a geographic distribution focused on the ancient Silk Road from the Far East (Korea and Japan) through the Middle and Near East (Iran to Israel) and is also found in North Africa (Choukri, *et al.* 2001). Genetic analysis indicates that the disease is associated with HLA-B*51, which is carried by 20 percent of healthy individuals (Arayssi and Hamden 2004). Other factors thought to mediate in its aetiology are infectious agents, immune

dysregulation, inflammatory mediators, heat shock proteins. oxidative stress, lipid peroxidation and environmental factors (Everekliogluu 2005). However, the relapsing and remitting nature of the disease makes it hard to study. The arthritis involved is generally mild, self-limiting and non-destructive (Smith 1982).

Musculoskeletal findings occur in almost half of all patients with Behçet's disease (Saylan, *et al.* 1999), but females are more commonly affected than males (Kim, *et al.* 1997). These are manifested as either painful joints or actual arthritis. Monoarthritis and oligoarthritis are the most common manifestations of arthritis and in the latter, the joints are normally affected bilaterally (Saylan, *et al.* 1999). The most commonly affected joints are the knees, ankles, hands or elbows, but small joints of the foot can also be affected (Yurtkuran, *et al.* 2006). Normally, the arthritis resolves itself rapidly, in days or weeks (Saylan, *et al.* 1999). Hand involvement can involve terminal phalanx tuft atrophy, and findings common in rheumatoid arthritis, such as swelling of the proximal interphalangeal joint and erosions and swelling of the wrists and ulnar deviation are seen. However, no degenerative joint changes were found (Yurtkuran, *et al.* 2006) and radiological examination of joints demonstrated no findings in the majority of cases (Kim, *et al.* 1997). Differential diagnosis of Behçet's disease includes Reiter's disease and enteropathic arthritis. However, several cases of ankylosing spondylitis have been noted coinciding with Behçet's disease, leading some to question whether Behçet's disease is part of the spondyloarthropathy spectrum (Etaouil, *et al.* 2002), but this may be a case of two diseases occurring at once (Chang, *et al.* 2002). Other diseases include Stevens-Johnson syndrome and pemphigus (Saylan, *et al.* 1999).

5.9.6 POEMS Syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein and Skin Changes Syndrome)

POEMS syndrome is the abbreviation for polyneuropathy, organomegaly, endocrinopathy, M-protein [also called monoclonal gammopathy (Rehmus and Kimball 2005)], and skin changes. This is a rare plasma cell dyscrasia of unknown

aetiology (Dispenzieri, *et al.* 2003) with only a few hundred cases described (Rehmus and Kimball 2005). Median life expectancy is around eight years, and it generally affects those in their fifth or sixth decade of life (*ibid.*). Although the disease name highlights non-skeletal changes (and reflects the diagnostic criteria for the disease), sclerotic bone lesions are common, occurring in 97 percent of patients in one study (Dispenzieri, *et al.* 2003). Lytic lesions have also been described, which are caused by osteosclerotic myeloma (Rehmus and Kimball 2005). However, Dispenzieri and colleagues (2003) described these lesions as having a sclerotic rim. Clubbing of the fingers is also a feature and found in approximately 13 percent of patients (*ibid.*). Proliferative enthesopathies are common, particularly in the posterior elements of the spine and around the sacroiliac and costovertebral joints (Resnick 1988c). So far, no cases of POEMS Syndrome have been reported in the palaeopathological literature.

5.9.7 X-linked hypophosphataemia

X-linked hypophosphatemia is a rare disorder with a prevalence of 1 in 20,000, and involves the mutation of the PHEX gene (Econs 1999) causing hypophosphataemia and low 1, 25- dihydroxyvitamin D concentrations (Yu and White 2005), whereas serum calcium, parathyroid hormone and serum calcitrol concentrations are normal (Econs 1999). Although the hallmark of the disease is non-skeletal (it involves renal phosphate wasting), skeletal disturbances are common. These include short stature, rickets, and dental abscesses (Econs 1999; Pitt 1988). There is a general increase in bone density in adulthood, especially in the axial skeleton and this relates to the fault in the mineralization process (Pitt 1988). Osteomalacia and fractures are also common (Yu and White 2005). Proliferative enthesopathies are common at tendon, ligament and joint capsule entheses of the axial and appendicular skeleton, particularly in the paravertebral ligaments and annulus fibrosus (Pitt 1988). Although the radiographic findings are distinctive, this disease does not seem to have been described in the palaeopathological literature.

5.10 Summary of Diseases

The aims of this chapter were to describe diseases which cause enthesopathy formation for the differential diagnosis of these from pathological changes with a traumatic aetiology. A further aim was to create better palaeopathological criteria for their diagnosis and to raise awareness of the many diseases which can potentially cause enthesopathies. To achieve this clinical and palaeopathological literature were reviewed.

It became clear early on, that the SpA are the most common diseases in this category (*i.e.* the category of enthesopathy forming diseases). Clinical diagnostic criteria and radiological data indicated that diagnosing the individual diseases in this group (*e.g.* AS and PsA) in archaeologically derived skeletal remains would prove difficult. For this reason new criteria based on clinical criteria for the diagnosis of SpA were created for palaeopathological use. It was also discovered that there are many diseases which have been linked in the clinical literature with enthesopathy formation. Some of these diseases are rare and it is possible that the presence of enthesopathy in these individuals is an incidental finding and may be caused by mechanical stress. Enthesopathy formation has only been investigated in detail in the SpA. Further clinical research is required into enthesopathy formation in the other diseases presented in this chapter. Table 5.14 presents diseases associated with enthesopathy presence in the clinical literature along with other skeletal involvement to aid differential diagnosis in archaeological skeletal remains.

Table 5.14 List of diseases reviewed, including theirskeletal involvement.

Disease	Enthesopathy location	Joint involvement	Other skeletal involvement
Seronegative spondyloarthropathies	Proliferative: any, but particularly, calcaneus (and other appendicular sites), spinal ligaments	Asymmetric oligoarthritis, appendicular arthritis, apophyseal joint.	Sacroiliitis, pencil-in-cup phalangeal deformity
DISH	Proliferative: anterior longitudinal ligament (spine), any appendicular enthesis (particularly pelvis,	Preservation of disc space	If sacroiliitis occurs there is no intra-articular ankylosis

Disease	Enthesopathy location	Joint involvement	Other skeletal involvement
	calcaneus, tarsal bones, olecranon of ulna, and patella)		
Fluorosis	Proliferative: any	Vertebral osteophytes	Osteosclerosis, periosteal bone thickening, change in bone density.
Lyme Disease	Proliferative: enthesitis occurs, but enthesopathy seems rare	Inflammatory monoarthritis typically of the knee, or less commonly degenerative joint disease	None
Ochronosis	Proliferative: pelvis, calcaneus, femoral trochanters. Degenerative: any	Paucity of osteophyte formation, calcification of vertebral disc, large joint involvement	Blackening of cartilages
Acromegaly	Proliferative: calcaneus, patella, femoral trochanters, tuberosities of the humerus, inferior surface of clavicle	Widening of joint space with osteophytes (typically knee, hip and shoulder)	Cranial and hand/foot hypertrophy. Endochondral bone formation at bone cartilage junctions
Ossifying diatheses	Proliferative: any	Osteophyte formation	
Leprosy	Calcaneal spurs (proliferative)		Disfigurement of face and pencil-in-cup deformities of hands and feet
Hyperparathyroidism	Degenerative: femoral trochanters, ischial tuberosities, humeral tuberosities, calcaneus, inferior clavicle surface, proximal ulna		Long bone curvature, cortical thinning
Hypoparathyroidism	Proliferative: posterior paraspinal ligaments, pelvis	Apophyseal joint calcification, intervertebral disc space preservation	
Hypothyroidism	Reported as a disease involving enthesopathy formation by Cush and Lipsky (2001)		
Behçet's disease	Enthesopathy, not linked necessarily to affected joints	Knees, ankles, hands, elbows – either monoarthritis or oligoarthritis.	Terminal phalanx tuft atrophy (hand)

Disease	Enthesopathy location	Joint involvement	Other skeletal involvement
		Erosions of wrists	
POEMS syndrome	Proliferative: any. Especially posterior spine		Sclerosis, clubbing of fingers
X-linked hypophosphatemia	Proliferative: any		Short stature, rickets, osteomalacia, fractures