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## Paget's Disease: Another Paramyxovirus in the Archaeological Record

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**Abstract:** The etiology of many human diseases remain unknown. There is often a tendency to imagine that insight into this area can only come from systematic scientific investigation into contemporary societies. However, there is often a wealth of data available in more distant records, including palaeopathological evidence, which, if considered in a critical manner, may provide clues not accessible in any other way. An example of this line of reasoning is provided in the discussion below, with particular reference to a disease of bone mineralization called Paget's disease. While there are a number of known causes of defects in bone mineralization, contemporary thought speculates that this particular disorder may be associated with chronic infection caused by a virus related to the paramyxovirus family. Palaeopathology, it will be argued, can provide an extraordinarily powerful tool, making testable predictions which may help resolve the issue of the possible infectious etiology of this disorder in a manner not easily approachable by other means. The value of this approach, in comparison with more (modern) sophisticated technologies such as probing for evidence of DNA sequences in Paget's bone with homology to paramyxovirus DNA sequences, is also considered.

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### Introduction

In the study of palaeopathology investigators analyze the evolution of disease through time and attempt to determine how past human populations adapted to their environments (Nelson *et al.* 1992). This detailed examination of diseases can often shed light on the factors which may be causally associated with their occurrence in earlier populations. Such insight comes from contemporary knowledge of possible etiologies of disease, in conjunction with archaeological evidence concerning various aspects of the cultures of the populations studied, including for instance, insight into their subsistence patterns and religious practices. In the essay that follows, I will outline the methodology of this process using, as an example, an investigation into Paget's disease.

I begin with a brief consideration of what Paget's disease is, who it affects, where it is most common, and what the clinical manifestations of the disease are. I then discuss the problems of differentiation between Paget's disease and other bone diseases using archaeological records. An example of a case study in which an attempt was made to distinguish between Paget's and other diseases is reviewed. Finally I critically assess the palaeopathological evidence which would support a role for paramyxovirus in the etiology of Paget's disease. Evidence consistent with this etiology would be an association between signs of Paget's disease and the introduction of paramyxovirus virus into human populations (past and present), in this case, it will be suggested, through contact with dogs carrying the distemper virus. Such information would be useful to anthropologists attempting to understand the evolution of human disease, and the

effect the introduction of such diseases may have had on past human societies. This data is examined in the context of the reasons for the existence and persistence of certain 'aspects' of culture (e.g., the domestication of animals, specifically dogs). The discovery of such data might serve a wider medical purpose in assisting researchers in the systematic documentation of evidence for infectious agents involved in certain diseases, which in turn contributes to the development of better treatment strategies.

### Description of Paget's disease

Paget's disease is a metabolic disease of bone, associated with extensive (hyperactive) remodeling of bone throughout the skeleton, with particular activity in the skull, spine and long bones (weight-bearing bones). This remodeling process is so "overworked" that it does not produce normal bone, but instead produces abnormally mineralized bone, lacking in strength. The precise etiology of the disease is unknown, although it is believed by some to be the result of a chronic viral infection with a long incubation period (latent virus). As will become more apparent below, palaeopathology provides support for this hypothesis as well as allowing us to speculate on the identity of the infectious agent. It seems likely that Paget's results from a chronic paramyxoviral infection. The paramyxoviral family is responsible for both the measles virus and the canine distemper virus. As noted below, there are contemporary epidemiological studies suggesting an association between measles, canine distemper virus and Paget's.

Paget's disease, or *osteitis deformans*, was first described in 1877 by Sir James Paget. The disease has since been characterized as a "general skeletal disease, frequently familial, of older persons in which bone resorption and formation are both increased, leading to thickening and softening of bones (e.g., the skull) and bending of weight bearing bones" (Stedman 1982:410). Although there are two other diseases referring to lesions of the breast and cancer of the vulva named after Paget, only the disease afflicting bone will be considered in this discussion of palaeopathology/methodology.

Paget's disease, which has also been referred to as "matrix metabolic madness" (Cotran *et al.* 1989), tends to affect older individuals (i.e., over the age of 50) and, today, is most common among populations in Europe, North America (where it has an incidence of 3%), Australia, and New Zealand (Camerlain and Myhal 1995). The disease is slightly more common among males than females, and is believed to be caused by a slow viral infection whose specific identity is unknown (Weatherall *et al.* 1983).

As was previously stated, the hallmark of Paget's disease is its excessive and localized resorption and formation of bone. Pagetic bone shows abnormal-looking osteoclasts (cells involved in normal bone resorption, but in Paget's disease are involved in the replacement of bone marrow by vascular fibrous tissue) with numerous nuclei which appear to be resorbing bone (Camerlain and Myhal 1995). As well, in this condition there is excessive osteoblast activity (cells involved in laying down new bone) which appears to be replacing the bone being absorbed with abnormal structures consisting of disorganized collagen fibres (Stirland 1991). The major anomaly in the disease is this large increase in bone turnover rate which results in a mosaic patterning of normal bone interwoven with deformed

(weak) fibrous bone. The bone is often also abnormally mineralized, as normal body physiology cannot maintain appropriate levels of calcium, phosphorus and other hormones intricately involved in the regulation of normal bone formation. Another characteristic of this disease is an overall increase in size of the various affected bones, in both the cortical as well as the trabecular bone, and a thickening of the trabeculae in their normal alignment (Mansfield and Rosenthal, 1993).

Paget's disease most commonly affects the sacrum, pelvis, spine, femora, and skull, but also occurs in other long bones (e.g., bowing of the tibia) (Weatherall et al., 1983). Patients afflicted with Paget's disease are lethargic and often suffer from other physiological changes, including an increased heart rate, high-output cardiac failure, warm skin, and sometimes localized pain (Roberts and Manchester, 1995). Most of these physiological changes are probably associated with providing increased vascularity and blood/nutrient flow to an area with a high metabolic rate (Paget's bone). Depending on the bones affected, more serious symptoms such as bone swelling, bone deformation (with resultant gait problems), osteosarcoma, osteoarthritis, and neurological symptoms, can develop (Camerlain and Myhal, 1995). With cranial involvement there is often an increase in size of the frontal prominence and patients may complain of headaches and even deafness due to alterations in the neurosensorial regions and mechanical pressure on the cranial nerves. Usually, however, this disease causes little physical discomfort to the victim and commonly goes undiagnosed until spontaneous bone fractures begin to occur in the affected region (Roberts and Manchester, 1995).

### Etiology of Paget's disease

As was previously stated, the behaviour of Paget's disease is similar to that of a slow viral disease. Some evidence of this comes from the fact that the disease has a late-onset and a high familial incidence. The risk of developing Paget's is seven times higher for first-degree relatives of an affected patient than in the general population (Stedman 1982). It is believed that the virus penetrates the genome of the osteoclast precursors during childhood and then manifests at a much later date. Other evidence which supports this conclusion is the discovery of virus-like inclusion bodies in the osteoclasts of patients with the disease. Nucleocapsids have been described in the nuclei and cytoplasm of Pagetic osteoclasts. These particles are similar to members of the paramyxovirus family, a group known to cause giant, multinucleated cell formation by induction of cell fusion in infected single cell populations (Camerlain and Myhal 1995). These observations have hence been thought to infer a possible relatedness of the viruses which supposedly cause Paget's disease and those which cause measles (another of the family paramyxovirus) (Youmans et al. 1987).

Another viral infection which may be related to Paget's disease and measles is canine distemper. In dogs, this virus causes premature death from resultant respiratory illness, in much the same way as does the human measles/rubeola virus. The distemper virus gains access through the respiratory tract, attacks lymphatic tissue, and then invades the bloodstream (Youmans et al. 1987). Evidence for productive infection with the distemper virus is limited to animals. However, observations made at the turn of the

century, which noted an increased incidence of measles among people who lived in close proximity to dogs infected with distemper, suggested a possible relationship between the two viruses (Schwabe 1984).

There is other evidence which suggests that some type of relationship exists between paramyxovirus infection in humans and dogs. In 1931, Nicolle reported an instance in which blood from a person who had been inoculated subcutaneously with the distemper virus actually produced distemper when injected into a young dog (Schwabe and Franti 1977), provided firm evidence that the canine virus can indeed survive in humans. Pinkerton *et al.* (1945, *cf.* Hull 1963), documented a similarity between the giant cell pneumonias and the inclusion bodies associated with measles, distemper, Hecht's diseases, and most interestingly, Paget's disease. A great variety of cross-infectivity experiments, (i.e., administering one virus to one population of animals and another virus to another population and determining the relative immunity of these groups to a third, related virus) have since been attempted and the measles vaccine has now been used to successfully immunize puppies against canine distemper. Although Hall *et al.* (1980, *cf.* Schwabe 1984) found that measles is more closely related to the rinderpest virus, and the canine distemper virus to PVM 107 (another paramyxo-Morbilli virus), they did conclude that there is some degree of relation between measles and canine distemper.

More recently it has been hypothesized that evidence suggesting a link between the measles virus and distemper, and between the measles virus and Paget's disease, may itself imply a causal link between Paget's and canine distemper. Preliminary studies have demonstrated evidence of a simultaneous occurrence of the two diseases in the same household (Camerlain and Myhal 1995). Based on these observations, further research is being conducted to determine the degree of relationship between Paget's disease and canine distemper. It is argued that such research should encompass palaeopathological studies of archaeological bone. The underlying hypothesis here being that if distemper is in fact causally related to Paget's disease, evidence for this disease should not appear in the archaeological record until the domestication of dogs.

### Identifying Paget's Disease in archaeological bone

Presently, Paget's disease is not uncommon, and can even coexist with other conditions including osteosarcomas in the elderly (Roberts and Manchester 1995). However, this disease has not often been identified in the archaeological record. This does not reflect the fact that it did not exist. The earliest identification of Paget's in archaeological bone dates to approximately 7000 BC (French Neolithic) (Roberts and Manchester 1995), but it is likely that this disease is present much earlier in the archaeological record, perhaps since the time of early domestication of animals (e.g., 10,000 to 20,000 years ago).

This lack of incidence of Paget's in past human populations is believed to be a direct result of a failure, in many cases, to differentiate Paget's disease from other conditions which produce similar pathophysiological changes in bone. If this differentiation is not made, palaeopathologies identified in archaeological bone may be incorrectly attributed to some other, similarly manifested disease. Some of the conditions which demonstrate a similar

radiographic appearance to that of Paget's include: osteomalacia (the adult equivalent of childhood rickets) (Roberts and Manchester 1995); hyperparathyroidism; Caffey's disease; intra-osseous hemangioma; bone neoplasms; lymphoma; Ewing's sarcoma; leukemias; fibrous dysplasia; and a variety of other infectious bone diseases including tuberculosis.

Paget's is perhaps most easily differentiated from lymphoma, Ewing's sarcoma, and the leukemias, all of which arise in the bone marrow and destroy the trabeculae as well as the cortex through infiltrative processes. These diseases tend to produce a moth-eaten appearance of the bone in the afflicted regions (Mansfield and Rosenthal 1993). While Paget's also affects the cortex and the trabecular bone, it is characterized by a generalized enlargement of bone (Weatherall *et al.* 1983) whereas the aforementioned (neoplastic) conditions are not. Paget's is also relatively easy to differentiate from bone neoplasms (malignancy in the bone tissue itself), because these diseases most commonly originate in the vascularized cancellous bone and again destroy the cortex at the site of tumor contact. An overall enlargement of the bone as a whole, which is a characteristic feature of Paget's disease, is not seen in bony malignancy. Fibrous dysplasia is characterized by randomly distributed fragments of trabecular bone in a fibrous stroma which results in a ground-glass appearance. Paget's disease is somewhat similar, producing thickening of the trabeculae, but in fibrous dysplasia the trabeculae are in their normal alignment (Mansfield and Rosenthal 1993).

Although other infectious bone diseases may at first appear to mimic Paget's disease, upon closer examination they can appear to be quite different. This is best demonstrated in Paget's disease afflicting the spine, where adjacent vertebrae are involved but there is no erosion of the endplates (as would be expected, for instance, in a tuberculous infection) (Mansfield and Rosenthal 1993). It is also unusual to see an infection affect both posterior and anterior elements of the vertebral bone as is common in Paget's disease. This becomes an important issue, for the palaeopathological record undoubtedly contains evidence documenting changes in the incidence of other chronic infectious diseases which affect bone (eg., tuberculosis).

In terms of metabolic bone disease, hyperparathyroidism may be confused with Paget's disease. However, closer examination of the radiology and biology of these two conditions allows the expert to differentiate between the two, based upon subtle differences in radiological appearance, bone density, and mineralization. Caffey's disease may also resemble Paget's disease but with scrutiny, a clear distinction can generally be made. Caffey's disease affects infant populations and is manifest as hyperostosis of cortical bone, while Paget's disease affects an elderly population and attacks both cortical and trabecular bone (Camerlain and Myhal 1995). Another condition which is often confused with Paget's disease is that of intra-osseous hemangioma. Intra-osseous hemangioma is a sclerotic and monostotic vertebral lesion (also common in the skull and, more rarely, in the epiphyses of long bones) similar to Paget's disease of the spine (Boyd 1970). Discrimination between the diseases often relies upon detailed examination of other bones which are not normally affected by intra-osseous hemangioma. Evidence for involvement of these bones is suggestive of Paget's disease. In archaeological bone, osteomalacia may be the

pathology most frequently misidentified as Paget's. Even in contemporary societies it is often difficult to distinguish between these diseases, which share many clinical manifestations. However, osteomalacia takes root in the vascularized cancellous bone while Paget's also affects the trabecular bone as well as destroying the cortex (Weatherall *et al.* 1983).

It is important to realize that data which help to discriminate between different diseases in living populations, for example enzymes and hormones related to bone turnover, are not available to the palaeopathologist. Therefore, differentiation between the various metabolic bone diseases must consider the context in which the bones were found. For example, bones appearing to be Pagetic in nature but found in regions of little sunlight (e.g., far north or south) are more likely to be due to rickets or osteomalacia. This is because of the fact that in such regions, very little vitamin D is present (humans rely on sunlight for chemical conversion of agents necessary for absorption of calcium from the diet) (Roberts and Manchester 1995). In an age when exogenous vitamin supplementation was not available, little calcium would be absorbed, resulting in diseases such as those stated above (but not Paget's disease). Another example of how context can effect diagnosis and differentiation is in populations living in areas associated with a high local aluminium content. Again such groups would be more likely to suffer bone mineralization defects because of competition between calcium and aluminium for absorption in the gut (Gilbert and Mielke 1985), and similar cation competition in other areas of body calcium physiology (leading to poor mineralization of bone, with calcium replaced by aluminium; abnormal parathyroid gland activity, renal disease, etc.). Also individuals who suffer from chronic renal failure, that live in areas of excessive salt intake, or have genetic predisposition to hypertension, etc., would in consequence also have low chemical conversion to produce vitamin D (a process occurring in the kidneys) and would again be more prone to developing osteomalacia (with below normal calcium uptake in the diet).

Having discussed processes involved in the identification of Paget's disease, it is perhaps prudent to give an example of such a case from the archaeological record. Stirling (1991) describes the rare pathological lesions found in a middle-aged male from the Norwich medieval church of St. Margaret (1468 AD). Stirling concludes that this male represents a classic case of Paget's disease. This diagnosis is based upon the detection of the thickening of many of the bones that are typically affected by Paget's disease. Fibrous dysplasia could be ruled out as a cause because there is no evidence for bowing deformities or a "ground glass" appearance. New periosteal bone formation, which is characteristic of other diseases, is also lacking. Lastly, because of the involvement of the epiphyses and the advancing wedge of radiolucency, Stirling concludes that the individual represents a classic example of *osteitis deformans* in the archaeological record.

### Reconstructing the etiology of Paget's disease using palaeopathological evidence

It should be possible to use palaeopathological studies of human bone to test the hypothesis that Paget's disease does in fact represent some form of a paramyxovirus, and that it is related to the paramyxovirus causing canine distemper. In order for this

hypothesis to be accepted, the following conditions must be apparent in the archaeological data. First, it must be assumed that, because to date the earliest record of Paget's disease only dates to the Neolithic period, there may have been a misclassification of Paget's disease in earlier populations due to an inability/failure to differentiate between it and other metabolic bone diseases which mimic its symptomatology. This is a necessary assumption because, if the Neolithic specimen from Lozère really is the earliest case of Paget's disease, then it is difficult to argue that this is a disease attributable to human infection with a canine distemper virus because the introduction of dogs living in close proximity (domestication) occurred much earlier (10,000-20,000 years ago). Accordingly, if the etiology of Paget's disease is an agent causing existing disease in another species, in this case dogs, which crosses the species barrier to infect the human population, we might anticipate evidence for Paget's disease at some time after the domestication of dogs. A contemporary equivalent would be the notion that AIDS represents human infection with a non-human primate virus. *Ad hoc* hypotheses might still rescue the theory if we assume that what is now an infection of dogs (canine distemper) was in earlier times a viral infection of another extant species which cross-infected humans, or even if we assume that some other co-factor(s) were necessary for the cross-species transmission of the distemper virus, and that the co-factor(s) did not appear in the archeological record until the Neolithic period.

Second, if Paget's disease is somehow causally affiliated with the virus inducing canine distemper, then we would not expect to see an appearance of Pagetic bone prior to the domestication of dogs (i.e., 10,000-20,000 years ago) (Cohen and Armelagos 1984). Furthermore, there is independent data from contemporary populations, referred to above, showing an increased incidence of Paget's disease in individuals living in close proximity with dogs. One would thus expect to see, in the archeological records of different populations, a higher incidence of Pagetic bone in individuals from domesticated societies living in close proximity to dogs, as compared with those from non-domesticated populations (no close proximity to dogs) of the same time period.

If these two conditions (Paget's disease and canine distemper) are related by etiology as well as epidemiology, then both must be present in any one population at a given time for cross-infection to occur. Thus there should be evidence, in canine skeletal remains found in proximity to populations demonstrating independently an increased incidence of Paget's disease, for death from, or death occurring with, respiratory disease associated with distemper infection. Such evidence might take the form of signs of bone pathology associated with chronic infections of the respiratory tract (e.g., rib-cage fractures, bone distortions, etc.). It could also be argued that Paget's disease should occur, at least initially, in human groups inhabiting those geographical areas where the dog population is at an increased risk of developing canine distemper. The risk factors for distemper are unknown. So too is the initial agent or primordial virus from which canine distemper in dogs originated. Further scientific investigations involving the evolution and epidemiology of this particular family of viruses, the paramyxoviruses, may provide some assistance in investigating this part of the archaeological record.

Lastly, we should bear in mind the possibility that there may be no increase in the prevalence of Paget's disease in the archaeological record, and/or that a re-examination

of bones may fail to differentiate between it and other metabolic diseases of the bone. This, however, would not necessarily invalidate the hypothesis that Paget's disease is caused by canine distemper virus or a closely related virus. It appears evident that Paget's disease has a long incubation period, and thus if it is a virus-induced disease, it is due to a slow virus. Thus the best evidence for a correlation in the archaeological record would necessarily come from the elderly individuals in any population. Because we cannot as easily identify unequivocally examples of early Paget's disease (e.g., in younger individuals) we may fail to see the correlation, and conclusive statistical data may be lacking simply because there are not enough specimens of elderly individuals with the full-blown disease. For this reason, it may be useful to develop other independent ways of identifying the existence of Paget's disease in populations of individuals. One example of such a method is through an examination of other artifacts associated with these populations which may provide independent evidence of the existence of a disease leading to the bone deformations characteristic of Paget's disease (e.g., graphic depictions in local art work may emphasize large foreheads or denote neurological afflictions, both of which are associated with Paget's disease) (Nelson *et al.* 1992). Another more sophisticated methodology which may be used today involves developing a DNA test (e.g., determining an independent genetic marker for the disease) which can be used on archaeological bone (Waldron 1994). Using DNA extracted from well preserved material of earlier human populations, it may then be possible to find evidence for both the presence of individuals with a Paget's disease susceptibility locus, and simultaneous domestication of animals, in a test population suspected of showing an increased incidence of Paget's disease. Note that such a test would be limited by the relatively minute amounts of DNA extractable from bone tissue (predominantly a mineralized tissue). An alternative test would look directly for DNA evidence of the presence of a virus with homology to canine distemper in recovered tissue derived from populations suspected of showing bone demineralization diseases.

### Summary

Paget's disease, although similar to many other bone diseases, has many distinguishing characteristics which allow its independent differentiation and classification in the archaeological record. It is important to note that the archaeological context in which bony artifacts are found plays a critical role in this differentiation process and, if ignored, can result in the misclassification of much fossil evidence. Although the exact cause of Paget's disease is to date unknown, there is general agreement that it may be related to infection with a slow virus. Some recent studies suggest that Paget's disease is a result of infection with a member of the paramyxovirus family. If this is true, as pointed out above, there are many implications for palaeopathology. It may even be the case that some of the best data which might point towards the etiological agent involved in Paget's disease actually lies encased in material from human populations of thousands of years ago!

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