University of La Méditerranée – Aix-Marseille II
Faculty of Medicine, Marseille, France

University of Szeged
Faculty of Sciences, Szeged, Hungary

PH.D. THESIS

"ON THE TRACES OF TUBERCULOSIS"

DIAGNOSTIC CRITERIA OF TUBERCULOUS AFFECTION OF THE HUMAN SKELETON AND THEIR APPLICATION IN HUNGARIAN AND FRENCH ANTHROPOLOGICAL SERIES

Márta MACZEL

Supervisors:
Prof. Olivier Dutour
Dr. Antónia Marcsik

UMR 6578 CNRS-University of La Méditerranée, Marseille, France
Department of Anthropology, University of Szeged, Hungary

2004

Introduction

The story of *infectious diseases* seems to be a never-ending one: as soon as an infection is eradicated, a new one emerges or an ancient affection re-appears usually in a renewed form. This latter, the re-emerging form of an infection is of particular importance, since it is alarming when a disease previously thought to be under control escapes human preventing measures and produces tissue alterations that are difficult to recognize in lack of up-to-date diagnostic criteria.

When an infectious agent (virus, bacterium or fungus) enters the human body directly or by mediated transmission, largely depending on the effectiveness of the host's immune system, the infection might result in death (especially in the case of viruses) or latent, acute or chronic diseases. Generally, the pathological changes due to the infection affect only the soft tissue; however, in a long-standing disease (chronic stage) bone changes also develop.

Based on the examination of skeletal alterations in human remains, *paleopathology*, having evolved from the study of medical curiosities more than 200 years ago, and its relatively new branch, *paleoepidemiology*, going beyond the casuistic descriptions by drawing conclusions on the population's level, provide invaluable information for the comprehension of the disease in the past as well as in the present. On the one hand, through the examination of skeletal series, we can gain information on the past populations' sanitary conditions and the evolution of the disease. On the other hand, paleopathological results can bring help in modern medicine by establishing new diagnostic criteria through the direct observation of bones, and provide information on the natural expression and development of the disease.

Paleopathological study of *tuberculosis* in osteoarcheological human remains is a little older than 100 years (Morse, 1967), but in the last two decades a considerable acceleration could be observed in the gaining of information on the disease. In fact, more and more evidence exists that tuberculosis has been a constant companion of man throughout history, and shaped human evolution by being the most significant population-regulating factor in the non-plague years. Moreover, it is one of the most important and dangerous diseases that are presently undergoing re-emergence: it seemed to be under control, but the number of new cases each year (often in association with HIV) and the appearance of multiresistant tubercle bacilli are warning signs that the disease might prove the opposite. Therefore, the understanding of the disease and its pathogen is a must to influence the way how TB will shape our life in the third millennium.

The study of tuberculous lesions in the human skeleton is of particular interest for several reasons. Although human TB, principally caused by two members (*M. bovis* and *M. tuberculosis*) of the pathogenic *Mycobacterium tuberculosis* complex (MTB), is primarily a soft tissue infection, clinical data show that in 3-7% of patients with chronic tuberculosis skeletal involvement can also be observed. The generated bone alterations consist of morphologically more or less characteristic lesions, with a particular predilection for certain skeletal locations. Being a common disease in the past and due to its relatively good detectability in ancient human remains (several thousand-year-old skeletons, mummies and calcified soft tissues), TB is one of the most well-known infectious diseases in paleopathology.

Furthermore, resulting from the TB bacilli's construction (having a rather resistant acid cell membrane envelop for protection) and the relative genomic stability, specific and efficient protocols could be developed for the detection of bacterial remains in ancient bones. The establishment of *paleomicrobiology* by the introduction of molecular biology into paleopathology opened a new chapter in the study of tuberculosis. The utilization of the new biomolecular techniques not only in individual cases but extended to population studies can furnish us with more appropriate epidemiological conclusions, too. It has to be noted that molecular biology is also enhanced by its "fusion" with paleopathology: skeletal series provide direct sources of information on ancient pathogens, their characteristics and evolution, factors that might efficiently contribute to the comprehension of the undeniable effectiveness of pathogenic mycobacteria and the present and future control of the disease.

Objectives

Although tuberculosis is one of the most thoroughly studied and well-represented diseases in paleopathology, a question is frequently posed: if TB was as common in the past as historical data suggest, why there is not sufficient direct evidence to see? During the current study, our principal objectives were theoretical elaboration on as well as actual detection of skeletal changes that might have been provoked by tuberculosis. For this reason, we provide syntheses on the newly described probable TB changes in different skeletal locations by reviewing their paleopathological literature, we consider further evidence from osteological materials, and present the results of our macro-morphological study, supported in a few cases by complementary data and analyses. With the utilization of the literature's data and the results of the examined series, our conclusions are to consider the differences in morphology, skeletal pattern (predilectional places) and age distribution.

Since till now the prevalence of TB in ancient populations came primarily from data on the paleopathological diagnosis of advanced-stage bone alterations (i.e. Pott's disease and large joint affection), another important objective of our work was the provision of more relevant disease frequencies concerning past populations keeping in mind the limitations originating both from the type of material and the utilized detection techniques.

Material and methods

For the study of tuberculous alterations, we selected *anthropological samples* comprising more than 800 skeletons, dated at the 6-18th centuries and coming from sites of Central Europe (Hungary) and the Mediterranean region (France). Furthermore, we utilized as a *reference series* a modern sample (150 skeletons) with diagnosed causes of death, dating from the beginning of the 20th century (CISC; Coimbra, Portugal). The choice of these skeletal materials can be explained by the urge to detect possible variations in the skeletal expressions of TB in different populations.

In some of the osteoarcheological samples, a thorough anthropological study has to be conducted (e.g. La Celle Abbey, Csongrád-Felgyő), while in others our task consisted only in the paleopathological re-examination of the series focusing on the lately determined diagnostic criteria (e.g. Bácsalmás-Homokbánya). In the current work, we summarized the series' historical and archeological backgrounds and analyzed the paleodemographical and preservational characteristics to provide a firm basis for the interpretation and comparison of paleopathological findings.

The examined human remains originate from populations with different life-styles and socio-economic conditions. However, in the interpretation of the paleopathological and paleoepidemiological results, we always have to keep it in mind that the examined skeletal populations generally do not correspond to the living population, and even the "dead population" can only be partially represented as a consequence of various factors (Dutour et al., 1998a-b; 2003). In fact, in the selected anthropological series various biases had to be considered. Although no specific burial assemblage could be noticed in the six examined osteoarcheological series, the CISC subsample, which originates from a hospital cemetery, is biased in its composition as a result of the missing infant and young child remains. Except for one series (Sándorfalva-Eperjes), the examined osteoarcheological samples come from sites that were not fully excavated. The time lapse of the series significantly differs, ranging from very precise dates (e.g. the skeletal material of Observance, including the victims of the Great Plague in Marseille in 1722) to several century-long periods (e.g. the series of La Celle, including burials from the late 6th to the 13th century). The state of preservation (quantitative and qualitative levels) proved to be considerably different in the various samples. Therefore, we chose a previously suggested method (i.e. provision of an observability index) for the inclusion of the preservation characteristics in the interpretation of our results. The selected formula was slightly modified in respect of three skeletal locations principally predilected for tuberculous changes (spine, ribs, and skull) in order to better appropriate the results (i.e. provide corrected TB prevalences).

Our work was essentially based on the exact and consequent description of skeletal changes observed during the *macro-morphological examination*. For the newly (re-)discovered criteria having a potential for diagnosing tuberculosis in skeletal series (i.e. vertebral hypervascularization, rib periostitis, diverse endocranial alterations and diffuse periosteal new bone formation), we introduced the term 'minor osseous lesions attributable to tuberculosis' (MOLAT) and gave a synthesis of the knowledge on them. Since the previously defined criteria appeared to be insufficient to describe all the observed morphological types of skeletal changes, we also applied a new term, 'stellate endocranial reaction' to designate a specific pathological alteration in the endocranial lamina.

To aid the diagnosis of the revealed bone alterations in the examined skeletal series, we utilized *complementary radiological and the most up-to-date molecular biological analyses*. Regarding the radiological examination we came to the same conclusion as Santos (2000) that the overall description of lesions could be better done through gross morphological observation, since X-ray in paleopathology is limited to sufficiently large lesions with adequate decalcification of bones, while subtle changes observed in dry bones are invisible in radiographs. However, the utilized paleomicrobiological methods represent powerful, new analytical tools, with which the detection of minute quantities of partially degraded bacterial remains became possible.

Results and discussion

Concerning **macro-morphological results**, we have to underline that in the examined skeletal samples the ***characteristic, advanced-stage tuberculous alterations***, on which diagnosis was mainly based even some years ago, such as Pott's disease and large joint tuberculosis were present only in a small number of cases. Furthermore, the apparently advanced-stage bone alterations in some cases showed a rather atypical form (e.g. CsoF-205), making their macro-morphological diagnosis less evident. This uncertainty could be overcome by the biomolecular confirmation of the presence of TB bacilli in the affected skeletal elements.

Minor osseous lesions attributable to tuberculosis were discovered in a much larger number of individuals. These early-stage bone changes have got into the spotlight only recently, and consist in *periosteal appositions on the visceral surface of ribs*, which seem to reflect pleuro-pulmonary tuberculosis in a large number of cases (Kelley and Micozzi, 1984; Roberts *et al*., 1994; 1998; Santos and Roberts, 2001), *endocranial changes*, often attributable to tuberculous meningitis (Hershkovitz *et al.,* 1998; Schultz, 1999; 2001), *hypervascularisation (severe circumferential pitting) of vertebrae*, proposed to be signs of early-stage spinal tuberculosis (based on the 19th century studies of Victor Ménard (1888) and the recent results of Brenda Baker (1999), and diffuse periosteal new bone formation, known under the term of *hypertrophic osteoarthropathy* (HOA), which appears to be a general skeletal response to intrathoracic disease, most often tuberculosis (Rothschild and Rothschild, 1998; Mays and Taylor, 2002). These alterations have been described as potential diagnostic criteria for TB, especially on the basis of the identified osteological collections' examination, such as the Hamann-Todd (Kelley and Micozzi, 1984) and Terry Collections (Roberts *et al*., 1994; Pálfi, 2002), and the co-occurrence of these conditions was also observed in the Coimbra Identified Skeletal Collection (Santos and Roberts, 2001).

It has to be noted that although there seems to be a strong positive correlation between these skeletal changes and tuberculosis, the original authors were very careful in considering them as pathognomonic signs of tuberculosis. Concerning *proliferative rib lesions*, Pfeiffer (1991) claimed that they could rather be interpreted as a non-specific indicator of chronic respiratory disease stress within a population. Rothschild and Rothschild (1998) as well as Mays and Taylor (2002) pointed out that *HOA* might be a non-specific indicator of intrathoracic infection. Hershkovitz *et al*. (2002) emphasized that certain endocranial alterations (e.g. SES) might refer to intrathoracic infection, not specifically TB. Since the prevalence of pulmonary infections in a population is an important indicator of lifestyle and health, therefore rib periostitis, endocranial lesions and skeletal changes of HOA can at least be considered as important indicators of health in archaeological populations.

If we look at our findings obtained by various detection methods in our skeletal material, the corresponding results reinforce the suspected tuberculous etiology in several 'MOLAT' cases. The frequent association of probable TB changes (in 32 per 128 individuals) and the assumption that *vertebral hypervascularization, endocranial changes* and *HOA* are all related to some sort of vascular anomaly refer to the fact that they might develop as a consequence of the same chronic infection. In fact, the frequent co-occurrence of the different types of *endocranial changes* (i.e. whitish discoloration, abnormal blood vessel impressions, *serpens endocrania symmetrica*, stellate endocranial reaction as well as the fine plates of new bone and sharply demarcated erosive defects) with one another as well as with other extra-cranial bone alterations often related to TB also leads us to pose the question whether they might have the same etiology (maybe tuberculosis) and they could represent different stages of the same disease process. In this way, their separation according to their morphology does not seem to be reasonable.

Although several pathological conditions have to be taken into account in the ***differential diagnosis*** of these bone alterations, the considered pathologies are basically not the same. Therefore, the probability that these lesions, often co-existing in the same skeleton, represent different disease processes is rather low, though not impossible. This latter fact might also stand behind some negative PCR results in the detection of MTB DNA. However, a large number of biomolecular analyses, especially that of vertebral hypervascularization, seem to support the tuberculous origin of these alterations. As it was previously pointed out, the examination of osteological collections with recorded causes of death also provided evidence for the frequent appearance of these osseous changes in tuberculous patients. Furthermore, since tuberculosis is a widespread disease today (according to the WHO's data, one third of the world's population, i.e. approximately 2 billion people are affected) and was also reported a common infection in the past, the large number of detected cases with such skeletal changes in osteoarcheological series might represent the same tendency and, therefore, TB may be favored in their differential diagnosis.

It is interesting to note that in our material the traces of possible skeletal infections were often accompanied by the so-called *stress indicators* (in at least half of the detected possible TB cases), which on the one hand, might be translated as decreased immune resistance to diseases in childhood, even if they were survived, and on the other hand, could be generated by the physiological troubles provoked by infection. Concerning this latter case, Pfeiffer (1991) emphasized that stressors could also exacerbate the progress of infectious disease and influence its course.

Regarding our **paleoepidemiological results** we can say that 128 probable TB cases were identified among the 826 skeletons belonging to the six examined osteoarcheological series. If we take a closer look at our data, a considerable difference can be seen between the number of cases detected due to the classical and the newly introduced diagnostic criteria, their utilization sometimes also coinciding in the same skeleton. In fact, due to the classical criteria only a small fraction, i.e. 17 individuals could have been revealed, while early-stage skeletal alterations were observed in 122 individuals (even in cases where advanced-stage bone lesions were present).

The 'MOLAT' appeared in all age groups, but they could be particularly seen in juveniles and young adults. A certain tendency could also be noted in the distribution of these early-stage bone changes. In the series of La Celle, where an outstandingly high number of endocranial lesions are present, the alterations can especially be observed in infants and young children. The skeletal population of Bácsalmás-Homokbánya, however, stands out with the exceptionally high representation of vertebral hypervascularization, which is particularly present in the *Juvenis* age group. These data might suggest particular, age-specific skeletal responses to the infection, but they may also represent population-characteristics since in the CISC subsample rib periostitis is overwhelmingly present, showing a more or less remodeled aspect in the affected individuals belonging to various age groups.

The frequent appearance of minor osseous TB changes in younger age groups directed our attention to the more detailed examination of child bones, though they are generally the least well-preserved in skeletal series. This idea led us to the thorough re-examination of the child skeletons in

the series of Bácsalmás, which are fairly well-preserved, but till now, unlike in the adults, no TB alteration was discovered in them. As a result of our morphological study, a high number of endocranial alterations were revealed both in subadults and adults, and were found often in association with vertebral hypervascularization, which is the most richly represented potential TB lesion in this series, also confirmed by biomolecular results.

Concerning the ***calculated and estimated TB frequencies*** in the examined Hungarian and French osteoarcheological series, we have to note that our data almost certainly contain large approximations. On the one hand, our results probably *underestimated* in several ways the prevalence of the individuals who suffered from TB in the past populations. The reasons come from the nature of the disease, the examined material and the scientific field. On the other hand, in all probability we also *overestimated* the prevalence, since we bravely suggested the tuberculous etiology of pathological changes, though in many of the detected cases the diagnosis could only be based on analogous reasoning with similar cases previously described in anatomical collections with recorded cause of death and/or the frequent association of potential TB alterations.

During the paleoepidemiological evaluation of the results, the deficiency of the utilized formula to provide *corrected TB prevalences* was also noted. Our conclusion concerns the prudent application of an observability index for correction, especially in the case of diseases like tuberculosis, where virtually the whole skeleton can be affected and age-specific alterations might also appear. In fact, in series with low observability of the TB-predilected skeletal locations but high representation of probable tuberculous changes, we unreasonably increase the calculated TB prevalence with the implication of skeletal preservation. The establishment of formulae for the more precise evaluation of TB prevalence, including the paleodemographical characteristics of the series, the presence and type of probable tuberculous lesions as well as the skeletal preservation, is highly awaited in paleoepidemiology. Besides the theoretical problems of prevalence calculation, comparison of the frequencies obtained in our skeletal samples is difficult due to the various biases in the study of skeletal populations. Comparison with other paleoepidemiological studies is further limited, resulting from the lack of clarified diagnostic criteria and standardized methodology as well as from the oft-missing background information on the series.

All the same, the TB prevalences calculated during this study seem to be consistent with other recent results, which showed that for the more appropriate estimation of past TB affection, the application of new criteria and detection methods are unavoidable. Regarding the choice of the examined skeletal material, we can say that we set out to detect possible variations in the skeletal expression and prevalence of TB in different populations. Our findings attest that the potential tuberculous skeletal lesions were present in all of the examined skeletal materials in a similar form in the predilected skeletal locations. The revealed differences in predominant lesion types and detected TB frequencies seem to be rather due to population characteristics and most likely to socio-economic conditions (e.g. the endogamic population of Bácsalmás-Homokbánya, the medieval population of La Celle where tuberculosis must have been endemic in the subsequent generations, and the urban population of Observance stricken by famines) than reasons purely deducible to geographical location or chronological period.

Concerning the **paleomicrobiological analyses** we have to note that in 66 individuals coming from the six osteoarcheological series the 123 bp segment of the insertion sequence IS6110 was used to detect TB infection. However, in the CISC subsample we could also refer to HPLC examination of mycolic acids besides the detection of MTB DNA (Santos, 2000). In our analyses, controls enabled us to exclude the possibility of false-positive results. Moreover, care was also taken in the interpretation of negative results. The largest number of positive PCR results, were gained from the advanced-stage TB cases. The analyses of MOLAT yielded various findings, but confirmed in many cases (particularly, in those of vertebral hypervascularization) the presence of TB bacilli in the affected skeletal elements. The negative results might be explained among others by degraded aDNA, the absence of directly invading mycobacteria and even the misdiagnosis of the detected bone changes.

The *hematogenous spread* of TB bacilli has already been proved by the identification of bacillus DNA both in pathological and normal tissues of the same individual (Faerman *et al*., 1997). In our material, similar analyses have also been carried out. Concerning the examination of pathological alterations developed at different skeletal sites, as well as normal tissues from otherwise affected individuals confirmed the hypothesis of hematogenous spread in individuals coming from the series of La Celle and Bácsalmás.

It has to be emphasized that pathogenic mycobacteria could be detected even in *seemingly unaffected bones*, attesting a greater range of exposure to the infection or disease without osseous changes. In fact, the biomolecular analysis of 18-19th century naturally mummified individuals ('Hungarian mummy project'), originating from the crypts of the Dominican church of Vác (Northern Hungary), already provided molecular paleoepidemiological results showing a very high rate of exposure to the infection (55%) in Hungary and in several cases the association of positive PCR results with gross pathology. These analyses also demonstrated that the detected pathogenic mycobacteria were more closely related to present day *M. tuberculosis* than to *M. bovis* (Pap *et al.,* 2002a,b). Concerning the characterization of the infective pathogen, the analyses of Taylor and his collaborators (1999) also showed that TB bacteria responsible for the medieval infection in England were more closely related to present day *M. tuberculosis* than to *M. bovis*.

The differentiation of the two main human infecting mycobacteria (*M. bovis* and *M. tuberculosis*) is a topical question in paleomicrobiology. Theoretically, it is also possible that such a member of the MTB complex caused infection that is currently absent in the studied geographical area but might have been present in historical times (*M. africanum*). Moreover, it is important to bear in mind that the DR region, used for the characterization of the pathogen, may not remain intact in all samples and that the spoligotype patterns can reflect differences in the preservation of the DR region rather than genuine differences in genotype. In our study, due to aDNA degradation only incomplete spoligotyping patterns could be gained, which however seem to reflect important information on the infective agents. In fact, our *spoligotyping* results in the 16-17th-century series of Bácsalmás-Homokbánya appear to reveal patterns rather resembling the bovine type bacteria, however at the present state it cannot be clearly stated whether the obtained data represent an ancient strain of *M. bovis* or maybe *M. africanum*. For a more precise conclusion making on the pathogens, further analyses and the utilization of other genetic markers seem to be essential.

Conclusions

As a conclusion, we can say that our results provide an insight in the past of tuberculosis, by reviewing and summarizing the literature on its origin, spread and development as well as by furnishing paleopathological evidence, paleoepidemiological data and paleomicrobiological confirmation through the examination of various anthropological series. The issues highlighted in the thesis are hoped to provide a backdrop for understanding the disease and maybe for establishing new approaches to its diagnosis and treatment. In any case, the old macro-morphological criteria and examination methods seem to be insufficient for the detection of TB cases in skeletal populations. The advent of new criteria having a potential for diagnosing tuberculosis and the application of the latest biomolecular techniques are proved to be pivotal to unravel the path of the disease.

Although much has been done, the analyses must continue on a larger scale and with the development and integration of more precise diagnostic criteria and examination methods. It cannot be neglected that osteological collections with recorded causes of death provide invaluable reference for the identification and characterization of the disease, but due to previous diagnostic inaccuracy care has to be taken in the interpretation of these results. The adequate solution seems to lie in the collaboration of anatomo-pathologists, microbiologists and paleopathologists, proving the utility of a multidisciplinary approach to tuberculosis, which is one of humanity's most successful predators.

PUBLICATIONS

Publications related to the dissertation

Maczel (M.), Marcsik (A.), Dutour (O.), Pálfi (Gy.), (1998): Palaeoepidemiology of tuberculosis in Hungary: preliminary results. *Acta Biol. Szeged*, 43: 103-109.

Ardagna (Y.), Aycard (P.), Bérato (J.), Leguilloux (M.), Maczel (M.), Pálfi (Gy.), (1999): Fouilles d'urgence et sondages archéologique à l'abbaye de La Celle, Var. *Travaux du Centre Archéologique du Var 1999*: 159-233.

Maczel (M.), Ardagna (Y.), Aycard (P.), Bérato (J.), Zink (A.), Nerlich (A.), Panuel (M.), Dutour (O.), Pálfi (Gy.), (2001): Traces of skeletal infections in a French medieval osteoarcheological sample (La Celle, Var, France). *Journal of Paleopathology:* 167-177.

Maczel (M.), Dutour (O.), Ardagna (Y.), Panuel (M.), Zink (A.), Nerlich (A.), Pálfi (Gy.) *(submitted)*: La série médiévale de l'Abbaye de La Celle, Var: Données anthropologiques et paléopathologiques. *Actes du colloque de GALF 2001.*

Maczel (M.), Molnár (E.), Marcsik (A.), Dutour (O.), Nerlich (A.), Zink (A.), Pálfi (Gy.) *(submitted)*: Paleoepidemiological data of skeletal tuberculosis from Hungary. *International Journal of Osteoarcheology.*

Maczel (M.), Marcsik (A.), Dutour (O.), Nerlich (A.), Zink (A.) *(submitted)*: Atypical tuberculous alterations in an ancient skeleton confirmed by paleomicrobiological results. *International Journal of Osteoarcheology.*

Publications cited in the dissertation

Bello (S.), Signoli (M.), Maczel (M.), Dutour (O.), (1999): Evolution of mortality due to tuberculosis in France (18-20th century). *In:* Gy. Pálfi et al. (eds.), *Tuberculosis: Past and Present.* Golden Book/Tuberculosis Foundation, Szeged-Budapest, p. 95-107.

Dutour (O.), Ardagna (Y.), Maczel (M.), Signoli (M.) (2003): Epidemiology of infectious diseases in the past. Yersin, Koch and the skeletons. *In:* C. Greenblatt et M. Spigelman (eds.), *Emerging pathogens. Archaeology, ecology and evolution of infectious disease.* Oxford University Press, Oxford-New York, p. 151-167.

Publications not included in the dissertation

Maczel (M.), Kocsis (G.), Marcsik (A.), Molnár (E.), (1998): Dental disease in the Hungarian Conquest Period. *Bull. et Mém. de la Société d'Anthropologie de Paris*, 3-4: 457-470.

Molnár (E.), Kocsis (G.), Maczel (M.), (1998): Entwicklungsanomalien der Zähne bei Skeletresten aus der ungarischen Awarenzeit von Pitvaros (Abstract). *HOMO*, Vol. 49/Suppl.: S68.

Piercecchi-Marti (M-D.), Adalian (P.), Bourliere-Najean (B.), Gouvernet (J.), Maczel (M.), Dutour (O.), Leonetti (G.), (2002): Validation of a radiographic method to establish new fetal growth standards: radio-anatomical correlation. *Journal of Forensic Sciences,* 47/2: 328-331.

Aycard (P.), Bérato (J.), Martos (F.), Maczel (M.), Pálfi (Gy.), (2002): Considérations sur deux têtes humaines coupées et inhumées isolément au Ier s. apr. J.-C. île de Porquerolles, Hyères, Var. *Bulletin Archéologique de Provence*, 28 : 29-37.

Dissertation-related conference publications

Maczel (M.), Marcsik (A.), Széplaki (L.), Pálfi (Gy.), Dutour (O.), (1998) : Osteotuberculosis in early and late medieval samples from Hungary. *Proceedings of the XIIth Meeting of the Paleopathology Association*, Prague-Pilsen, Czech Republic.

Maczel (M.), Ardagna (Y.), Aycard (P.), Bérato (J.), Zink (A.), Nerlich (A.), Panuel (M.), Dutour (O.), Pálfi (Gy.), (2000) : Traces of skeletal infections in a French medieval osteoarcheological sample (La Celle, Var, France). *Journal of Paleopathology (Abstract book - XIIIth Meeting of the Paleopathology Association,* Chieti, Italie), 11/2 : 71-72.

Zink (A.), Signoli (M.), Ardagna (Y.), Maczel (M.), Dutour (O.), Nerlich (A.), (2001): Molecular evidence for tuberculosis in vertebral bone tissue of burials of a plague cemetery. *Abstract book - ICEPID-4 ('International Congress of the " Evolution and Paleoepidemiology of Infectious Diseases "),* Marseille, France, p.73.

Dutour (O.), Signoli (M.), Maczel (M.), Ardagna (Y.), (2001): Intérêt du "modèle peste" dans les études paléoépidémiologiques. *Abstract book - ICEPID-4 (International Congress of the "Evolution and Paleoepidemiology of Infectious Diseases"),* Marseille, France, p.74.

Maczel (M.), Dutour (O.), Ardagna (Y.), Panuel (M.), Zink (A.), Nerlich (A.), Pálfi (Gy.), (2001): La série médiévale de l'Abbaye de La Celle, Var : Données anthropologiques et paléopathologiques. *Abstract book - Colloque du GALF*, Marseille, France, p.57.

Maczel (M.), Pálfi (Gy.), Ardagna (Y.), Panuel (M.), Aycard (P.), Bérato (J.), Zink (A.), Nerlich (A.), Dutour (O.), (2001): Archaeological, anthropological and palaeopathological study of a medieval rural population: the series of La Celle Abbey (France). *Pre-prints - XIVe Congrès de l'Union Internationale des Sciences Prehistoriques et Protohistoriques*, Liège, Belgium, p.320-321.

Maczel (M.), Marcsik (A.), Dutour (O.), Nerlich (A.), Zink (A.), (2002): Atypical tuberculous alterations in an ancient skeleton confirmed by paleomicrobiological results. *Abstract book - 14th European Meeting of the Paleopathology Association,* Coimbra, Portugal, p.93.

Molnár (E.), Maczel (M.), Marcsik (A.), Pálfi (Gy.), Nerlich (A.),Zink (A.), Dutour (O.), (2002): Paleoepidemiological data of skeletal tuberculosis from Hungary. *Abstract book - 14th European Meeting of the Paleopathology Association,* Coimbra, Portugal, p.108.