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Editorial

A Problem in Palaeopathology

The Origin of Thalassemia in Italy

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Summary. Palaeopathology makes possible investigations into the origin of diseases. So the aim of this editorial is to explore all the palaeopathologic remains supposed to be related to the origin of thalassemia in Italy. This last is a problem which has led to much speculation. Two theories have been proposed. The first sees the earliest evidence of thalassemia as going back to the upper Palaeolithic era, and the second suggests that thalassemia originated in Greece and spread to Italy when it was colonized by the Greeks between the 8th and 6th centuries B.C. The second view seems to be supported by the fact that at present the incidence of thalassemia is highest in the areas where ancient Greek immigration was most intense – Sicily, Sardinia, Calabria, Lucania, Apulia and the mouth of the Po.

The conclusion is drawn that all the skeletal remains showing porotic hyperostosis found so far in Italy are unable to provide a solution to the problem of the origins of thalassemia in this country, owing to the impossibility of reaching a clearcut decision as to whether to accept or reject a diagnosis of thalassemia. This difficulty derives from the fact that porotic hyperostosis is common to a large group of haematologic disorders involving erythroblastic hyperplasia, especially if the disease develops at an early age. So, it appears obvious that, when haematological findings are not available, data of other type should be considered in the attempt to identify – as far as possible exactly – the nature of the blood disease responsible for the skeletal changes in each case. Some main methodological principles are considered in order to make investigations more rewarding in future.

Key words: Palaeopathology – Porotic hyperostosis – Thalassemia.

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Eins der größten Rechte und Befugnisse der Natur ist: dieselben Zwecke durch verschiedene Mittel erreichen zu können, dieselben Erscheinungen durch mancherlei Bezüge zu veranlassen.

Goethe W., Schriften zur Naturwissenschaft

The term "palaeopathology" was coined to refer to the study of traces of disease in ancient human remains, by M.A. Ruffer (1913) when Professor of Bacteriology at the Cairo Medical School.

Palaeopathology has become a wide-ranging science covering the vegetable as well as the animal kingdom. Several previous publications have reviewed the field of animal and human palaeopathology in detail. The first proper survey was published by Moodie in 1923, and in 1930 a book by Pales provided the most thorough bibliography and discussion of palaeopathology up to the second world war. The next indispensable book-length survey and bibliography (updating the literature from about 1930 to 1944) was that of Sigerist (1951). Since then a fair number of valuable shorter reports on the subject have been published. Those of Brothwell and Goldstein are chapters in the book "Science in Archaeology" (Brothwell and Higgs, 1969). Two symposia have also appeared, edited by Jarcho (1966), and Brothwell and Sandison (1967). The quite recent volume by Steinbock (1976) offers a rigorously scientific approach to the diagnostic and inductive facets of ancient human pathology.

Impetus was given to palaeopathological studies by Cockburn, who founded the Palaeopathological Association in 1973; in Europe, international meetings were held in London (1976) and Turin (1978).

The essential precondition for such studies is, clearly, the availability of remains in a satisfactory state. Most ancient populations buried their dead underground; in this case only skeletal remains, at best, have come down to us. Others practised cremation, which leaves the investigator almost nothing to work on. Embalming is a rare practice, but it is of enormous importance, as it is capable of keeping even soft tissue in an excellent state, and has allowed much valuable work to be done on pathological findings. From a palaeopathological viewpoint, mummies offer incomparably more interesting material than the much more readily available skeletons, whether complete or incomplete, since these only yield pertinent data where diseases have produced bone lesions.

The ultimate purpose of palaeopathology is still a controversial topic. This science provides a valuable source of data for archaeology by offering insights into the vigour and way of life of a given people. Thus the connections between ancient Greek culture and the physical condition of its people have been explored by Angel (1946 and 1966). Other authors have considered palaeopathology as being ancillary to the history of medicine, and as being especially valuable in understanding prehistoric ages for which no written documents are available. In any case, as pointed out by Cockburn, palaeopathologic remains certainly offer useful material for an objective evaluation of the true state of medicine and its evolution during the historical epoch.

All this is undeniable but as a pathologist I consider that some other important expectations should be fulfilled by palaeopathology. It should be borne in mind that, in general, disease is the result of an interaction between man and his environnement. This is why it reveals influences affecting the living organism. Thus palaeopathology makes possible: (a) thorough analyses of the living conditions of our distant ancestors, (b) useful comparisons between past and present ecological situations, and (c) investigations into the origins of some diseases.

As bone remains are by far the commonest type of material available in palaeopathology, the scientist best equipped for such tasks is the skilled pathologist who has had a good training in the morbid anatomy of the skeleton. The methodology to be applied is that commonly used in morbid anatomy – careful macroscopic examination with photographic recording, possible X-ray examination, and microscopic analysis with microphotographic recording. The histological and histochemical techniques will be modified on a case-by-case basis to allow for the state of preservation of the remains.

Any pathologist investigating a problem in human palaeopathology is clearly dependent on the archaeologist for his material, but this dependence should never be passive. There should be close collaboration between the two, to allow all the data pertinent to burial to be recorded. This is essential in the case of hereditary diseases, because it is then vitally important to know the relationship between the sick individual whose remains are being investigated and the other presumed members of his family.

The aim of this editorial is not to give a brief general survey of human palaeopathology, but to explore a complex problem of wide interest to palaeopathologists – the origin of thalassemia[1] in Italy.

Gatto (1948, 1960) put forward the view that thalassemia was present in the palaeo-insular populations of Sicily as early as the upper palaeolithic era. Gatto's reasoning was based on findings at a site called the "Cave of San Teodoro", about 100 km from Messina on the Messina-Palermo road. The skeletal remains of five adults had been found there by Graziosi (1943, 1947). Three of the skulls were fairly well preserved and were frankly chamaeprosopic in appearance, while the fifth skeleton showed widespread osteoporosis, in a particularly marked form in the spine and the epiphysis of the long bones. The two hypotheses on which Gatto's view was founded were (a) that chamaeprosopis might regularly occur in thalassemia, on a racial basis, and (b) that thalassemia might be responsible for the osteoporosis observed in the fifth skeleton.

A radiographic and perigraphic study of skulls 1 and 2 from the San Teodoro site was carried out by Correnti (1967). The lateral radiograms of skull 1 showed interruptions about 2–3 mm deep in the upper outline of the parietal areas. As a whole, these irregularities could be considered to resemble in a somewhat milder form, the "brush-like" picture which is one of the most distinctive features of Cooley's disease.

[1] "Thalassemia" is used here to refer to all types of thalassemia, i.e., all types of hereditary haematological disorder induced by an insufficient rate of synthesis of one or more of the polypeptide chains contained in the haemoglobin molecule (Weatherall and Clegg, 1972). Of these types the commonest is β-thalassemia, whose homozygotic form is called Cooley's disease

Professors Graziosi and Correnti very kindly allowed me to examine skulls 1 and 5 from the San Teodoro site, which yielded the following results.

As reported by Graziosi, the right temporal bone and the base of skull 5 are missing. Restoration of the face is impossible, as only a few small pieces have survived. It is, however, easy to investigate the structure of the cranial vault, as there is a long fracture running through the right parietal bone, whose mean thickness is 5 mm. The outer and inner tables of the cranium can be made out, but the widening of the diploë makes them look rather thin. There is clear evidence of senility in the features of the skull, and this conclusion is supported by the thinness and overall structure of the cranial vault. The osteoporosis found in the skull and other bones appears to depend on senility, and radiology reveals no pathological findings peculiar to thalassemia.

Skull 1 from the same site, the remains of a youth of about 20, is well preserved. The frontal and parietal bones have intact outer surfaces, and there is no evidence of multiple perforation by small pores leading to the diploic spaces, as would be expected if the bone had been affected by Cooley's disease. Radiological examination revealed a widening of the diploic space, most clearly in the parietal area, and the outer table was poorly defined. There are some radial and linear figures of breakage in the outer table, which are hard to account for when the physical integrity of the bone surface is considered. No inhibition of pneumatization was traceable in the maxillary sinuses. This, too, does not correspond to what would be expected in thalassemia major.

To sum up, little support for the theory that thalassemia was rife in Sicily during the upper palaeolithic era can be drawn from the San Teodoro remains. It is true that thalassemia minor or a thalassemia trait could have been responsible for the widened diploic space and the vague definition of the outer table in skull 1 (Moseley, 1963; Sfikakis and Stamatoyannopoulos, 1963), but such features are common to all of the many illness involving mild erythroid hyperplasia of the bone marrow (Moseley, 1965; Ascenzi, 1957 and 1976).

Gatto's view that the origins of thalassemia in Italy go back to upper palaeolithic times was challenged by Maxia and Cossu (1950). They noted that no remains belonging to a period earlier than the neolithic era had been found in Sardinia, which now has the highest incidence of thalassemia in Italy. Their investigations on 395 Sardinian skulls kept in the Cagliari Anatomical Institute revealed no lesions peculiar to thalassemia. Maxia himself later contradicted his earlier statement (Maxia and Floris, 1961; Maxia et al., 1973; Messeri, 1969). In their anthropological papers these authors vaguely mention skeletal remains in Sardinia showing signs of porotic hyperostosis[2].

Very recently Germanà and Ascenzi (1979) studied the remains of skulls belonging to three human adults discovered at S'Isterri d'Olzu (Sassari) in

[2] "Porotic hyperostosis" is a term which covers any kind of bone lesion involving a symmetrically distributed increase in the volume of the skeleton associated with a rarefaction of the bone texture. Clearly such lesions may be induced by any disease which leads to an increase in bone marrow volume, since this brings about a rise in the capacity of the skeleton which allows it to accommodate the extra haemopoietic marrow. From a palaeopathological viewpoint, therefore, porotic hyperostosis is the only adequate proof of medullary hyperplasia, either primary or secondary, when the skeleton is the only material to have survived

Sardinia, going back to the Bronze Age. All the skulls show changes corresponding to a generic porotic hyperostosis, but none of them justify a certain diagnosis of thalassemia.

The thirteen skulls with "hair-on-end" appearance observed by Caponnetto in Sicily (1939) cannot be profitably discussed as the material cannot be dated with any certainty.

The second theory about the origins of thalassemia suggests that it first became common in Greece and spread to Italy during colonisation by Greeks between the 8th and 6th centuries B.C. (Silvestroni, Bianco and Alfieri, 1952). This view seems to be supported by the fact that the twentieth century incidence of thalassemia has been highest in areas where ancient Greek immigration was most intense – Sicily, Sardinia, Calabria, Lucania, Apulia and the mouth of the Po[3].

To inquire into the problem of whether thalassemia came to Italy from Greece, skeletal remains from the ancient necropolis in the Trebba and Pega Valleys were examined anatomically and radiologically by Benassi and Toti (1957). The necropolis was the burial ground of the population of Spina, a town at the mouth of the Po which achieved great prominence between 500 and 200 B.C. There is a consensus of opinion that the town was founded by the Etruscans but colonized by the Greeks not long after.

Benassi and Toti reported that the remains were from adults, but gave no statistical breakdown of their sample – of the numbers and ages of the individuals. Nor did they give information about anthropological data, though these were provided later by Marcozzi (1963) and Marcozzi and Cesare (1969). After examining the skulls Benassi and Toti found that the diploic spaces were widened, and showed a wide-mesh network of trabeculae, notably in the parietal bones. The outer table had normal compactness, but both inner and outer tables were abnormally thin. No spicules of radially arranged bones were observed, and no mention is made of lesions in the facial bones, apart from prognatism and protrusion of the zygomata. There was evident epiphyseal osteoporosis in the long bones.

It may be concluded that as Benassi and Toti investigated adult remains only and no features peculiar to thalassemia were revealed, the diagnosis of thalassemia is not justified.

More recently, at Gravina, in Apulia, an ancient skull whose features seem to call for a diagnosis of thalassemia was discovered by Perosa. It was lying among a heap of human remains below the floor of one of the "cave churches" of Southern Italy, so called because they were excavated out of tuff soil. The historical documents (Nardone, 1941), some of which give a detailed account of the visitation of Cardinal V.M. Orsini in 1714, along with the archaeological and architectural features of the site, allow us to conclude that all the bones date back to a period previous to 1700, but the skull's discoverer has as yet preferred not to apply the ^{14}C technique, to avoid altering its properties.

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[3] The distribution of thalassemia within Italy has changed appreciably since the second world war, because there has been heavy internal immigration from Southern Italy and the islands to Northern Italy

Professor Perosa generously allowed me (Ascenzi, 1975) to present this well-preserved skull to the "Premier Colloque Français de Paléopathologie" held at Lyon in 1973. The characteristics of the teeth, in particular, indicate that the subject was 13–14 years old. The lesions, which mainly affect the cranial vault, show a high degree of symmetry, with prominent parietal bossae separated by a furrow running along the sagittal suture. This could be described as a mild form of natiform skull. The same feature of prominence also affects the frontal bossae but less markedly.

The porotic nature of the external bone table is evident on both sides of the frontal squama, on both parietals and on a limited portion of the occipital above the crest. It takes the form of many small pores or empty columnar spaces which lead into the diploic spongious cavities. An area of bone tissue whose porousness closely resembles that of the cranial vault is found – again, symmetrically – on the lateral segment of the roof of the orbits. This is identifiable as the type of *cribra orbitalia* (Welcker, 1888) called trabecular by Nathan and Haas (1966). In addition, minute areas of very fine porosis without protrusion of the bone surface is found in the wings of the sphenoid and the nearby temporal squama.

As a histological examination of the pathological bone in transversal section would have required the removal of a segment of the cranial vault, and permission to do this was not given by Professor Perosa, a thorough radiological examination was performed. Porousness is clearly observed in the outer table, essentially the parietal bones, and the diploic spaces are enlarged. Moreover, the striated "hair-on-end" pattern characteristic of thalassemia is found in spicules of bone lying perpendicular to the outer table. Inhibition of pneumatization in the maxillary sinuses was revealed, too, by the increase in volume of the maxillary bone.

Thus the lesions found in the Gravina skull, the youth of the individual and the reduction of pneumatization in the sinuses all seem to indicate a diagnosis of thalassemia major. This skull, however, cannot contribute much to the solution of the problem of where thalassemia originated until an approximate date can be attributed to it.

In 1977, Ascenzi and Balistreri published the results of an inquiry into human bone remains found in Lucania, a region of Southern Italy whose colonization by Greeks has recently been thoroughly investigated (Adamesteanu, 1974). The bones, belonging to 227 individuals, had been unhearthed during archaeological excavations, and kept in museums or storehouses in the towns of Metaponto, Policoro, Matera and Melfi. They were well catalogued, with details about the sites where they were found, types of funeral equipment and chronology. Their chronology was, unfortunately, very inhomogeneous, and ranged from the 8th century B.C. to the 17th–19th centuries A.D.

Porotic hyperostosis was identified in four skeletons, all belonging to adult individuals. In the first, the only remain was a calvarium, which had been deformed and fractured after death. Archaeological elements indicated that it dated back to the 3rd or 2nd century B.C., and the funeral equipment suggested a Greek grave. The other three cases were dated as medieval. The cranial vault of each specimen revealed symmetrical osteoporosis, which was severest

in Cases 3 and 4. Here the external table had disappeared, or had at many points, been replaced by spongy bone; the maxillary sinuses were large, and no porotic hyperostosis was traceable in them. In Case 2 the rest of the skeleton was affected by severe diffuse osteoporosis without hyperostosis, but the distribution characteristic of thalassemia and other chronic haemolitic anaemias, where porotic-hyperostotic lesions commonly affect the posterior segment of the ribs, especially in adult life (Ascenzi, 1957 and 1976), was not found.

In summary, the inquiry into human remains unearthed at sites in Lucania has not yielded decisive evidence in determining whether thalassemia came to Italy as a result of Greek colonization. The only presumably Greek remain is a rather badly damaged cranial vault. This certainly showed changes produced by porotic osteoporosis, but it would be rash to draw the conclusion that this can be attributed to thalassemia. The age of the individual and the absence of other bone segments suggest that the presence of thalassemia is less than probable.

Apart from the impossibility of solving the problem of the origins of thalassemia in Italy, all the bone remains investigated so far raise the same difficulty – that of deciding whether a diagnosis of thalassemia is justified. This derives from the fact that the syndrome of porotic hyperostosis is found not only in thalassemia, but also in a wide range of other haematological disorders all of which include erythroblastic hyperplasia, especially if these develop when the subject is still young.

A list of these conditions has been compiled by Moseley (1965), even if, as stressed by this author, some diseases – malaria is one – have not been included. The subject has been reviewed by Ascenzi (1976).

The reference to malaria becomes meaningful when we consider its relationship to thalassemia, although the complexity of the problem of whether the first favours the second makes it impossible to enter into a discussion here. One possibility, however, which does deserve attention is that porotic hyperostosis may be produced in chronic malaria by compensatory erythroblastic hyperplasia. This was maintained by Chini (Chini, Paternò and Nicotra, 1938; Chini, 1939) on the basis of the close parallel between the bone lesions revealed radiographically in cases of chronic malaria and in those of thalassemia. This valuable suggestion could be investigated further by studying chronic malaria in countries where it is at present endemic. This would provide results conducive to the solution of several key palaeopathological problems, especially that of the origins of thalassemia, as Angel (1966 and 1967) has already noted.

Iron-deficient anaemia, especially when associated with protein deficiency is another condition capable of inducing skeletal deformities resembling those found in thalassemia, as recently reported and discussed by Lanzkowsky (1977). Porotic hyperostosis is also responsible for inducing skull deformities in rickets, according to Hamperl and Weiss (1955).

As haematological data are not normally available in palaeopathology, data of other types should be collected to allow the identification of the particular blood disease responsible for a given case of porotic hyperostosis, among the many conditions capable of inducing it.

Much can be done on archaeological sites to gather information pertinent

to family relationships. When graves are found side by side or more than one person has been buried in a single grave, a careful sifting of the evidence may show that some or all of the individuals concerned belonged to the same family or had married into it. Angel (1967), by investigating the porotic hyperostosis in bone discovered in a Middle Bronze Age cemetery at Lerna, Greece, produced the clearest evidence of such ties.

Additional evidence may come from anthropological analysis of the resemblances between bone specimens.

Another useful variable is the age of subjects with porotic hyperostosis. The probability that such lesions have been induced by thalassemia major is inversely related to the age of the subject, as lesions in this disease begin very early, sometimes at an age of only $4^1/_2$ months (Caffey, 1937), whereas in hereditary spherocytosis of Minkowski and Chauffard where the illness usually develops only after adolescence, the bone changes are not appreciable (Letterer, 1949).

Bones other than those of the cranial vault are another valuable source of information in deciding whether a diagnosis of thalassemia is justified. In particular, a volumetric increase in the maxillary bone, accommodating hyperplastic marrow but leading to the inhibition of pneumatization, is found very frequently in thalassemia major (Moseley, 1965), while in older children and adults, evidence of infarction or cortical thickenings in some of the long bones is usually found in sickle cell anaemia. It also appears that turricephaly occurs in a fairly high proportion of cases of hereditary spherocytosis, whereas it is not clear that other hereditary deformities, such as wide root of the nose, palatal abnormalities, polydactilia, brachydactilia, persistence of deciduous teeth in adults and misplacement of permanent teeth, are more frequent that in the population at large.

All the points mentioned above should be borne in mind when skeletal bone lesions point to porotic hyperostosis; otherwise no well-founded diagnosis of the specific disease responsible for this condition will be possible. On this basis no diagnosis of thalassemia may be confidently formulated about any of the skeletal specimens investigated so far in Italy, not even the Gravina skull. It is true that some of its features could certainly have been caused by thalassemia, but nothing is known about the family of this subject, and none of the other bones have been found.

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