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Perspective article

Perspectives on anemia: Factors confounding understanding of past occurrence

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ABSTRACT

Objective: This paper reviews factors confounding the understanding of the past occurrence of anemia. Using the evidence gathered, a framework is presented of ways forward to enable greater confidence in diagnosing acquired anemia in paleopathology, facilitating insights into longer-term perspectives on this globally relevant condition.
Results: To date, porotic lesions have been central to paleopathological investigations of anemia. The fact that porotic bone lesions are omnipresent and have multiple causes but are likely to have a relatively low, age-related frequency in individuals with anemia, a condition that will have been common in past communities, is confounding.
Methods: Establishing frameworks that move away from porotic lesions is proposed to facilitate higher levels of more accurate anemia diagnoses in paleopathology.
Significance: Acceptance of the fundamental principle that anemia may be better considered as a condition requiring metric evaluation of bone structures, supplemented by careful consideration of lesions, will advance understanding of acquired anemia in past communities. Such an approach would provide a clear basis for further consideration of congenital conditions causing anemia, such as sickle-cell disease and thalassemia.
Limitations: This paper simply opens the conversation on the better diagnosis of anemia in paleopathology; it starts the iterative process of achieving some consensus and progress on diagnosing anemia in paleopathology.
Suggestions for further research: Engagement with ideas presented, sharing data and development of metric parameters will assist in identifying the effects of marrow hyperplasia on bone, enabling more robust work on the important topic of anemia.

1. Introduction

Anemia matters. In its various forms, anemia is estimated to affect a quarter of the current world's population (Pasricha et al., 2013). The term anemia describes a broad group of conditions in which oxygen transported to tissues is reduced below a level that meets physiological needs (Brickley et al., 2020:201; World Health Organization, 2011). Worldwide, these conditions create significant health problems in current communities, with high levels experienced in women of reproductive age and their children (e.g., Stevens et al., 2013). The critical role of women and children as human capital and in shaping social well-being, contributing to political and economic development, and providing community stability are well documented and form a central part of recent World Health Organization discussions (World Health Organization (2016); Richter et al., 2017). Globally in low- and middle-income countries, anemia is still a significant determinant of poor health and the burden of the condition in women of reproductive age and children is still particularly high despite slight improvements (Owasis et al., 2021; Stevens et al, 2013). Given what we know about acquired anemia, the condition is likely to also have been present, potentially at high levels in past communities. The large-scale review of current communities by Owasis and colleagues (2021) highlighted the complexity of factors that feed into the prevalence of acquired anemia and the importance of context-dependent drivers of anemia etiology. In many past contexts, factors that can reduce levels of anemia, such as overall reduction in parity, access to nutritious food and achieving a healthy weight prior to pregnancy, will likely have been absent for many individuals. Paleopathologists therefore need to consider anemia at a site-by-site level.

Research on anemia in past groups started early (e.g., Moore, 1929;

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Wakefield et al., 1937; Angel, 1964; Zaino, 1964; Jarcho et al., 1965; Moseley, 1965), with continued involvement in debates by those with medical training and significant, sustained levels of interest amongst bioarchaeologists and paleopathologists. Currently, the primary approach to investigations of anemia in paleopathology is discussing porotic lesions. Nonetheless, despite extensive investigations of porotic skeletal lesions for close to a century (e.g., Williams, 1929; El-Najjar et al., 1976; Stuart-Macadam, 1987; Bľandová et al., 2023), there is still a lack of consensus on the diagnosis of anemia and the role of the porotic lesions, particularly those now widely referred to as cribra orbitalia (CO) and porotic hyperostosis (PH) (e.g., McIlvaine, 2014; Rivera and Mirazón Lahr, 2017; Brickley, 2018; Cole and Waldron, 2019; Anderson et al., 2021; Schats, 2021; Zdilla et al., 2022). There is a broad spectrum of opinion from those who take porotic cranial lesions as a marker of anemia (e.g., Rinaldo et al., 2019; Hens et al., 2019) to those who consider such lesions to be indicators of completely un-related conditions (e.g., Rothschild, 2012; Zdilla et al., 2022). The lack of consensus extends to the post-cranial skeleton; no agreement has been reached on what, if any, role porotic lesions in the post-cranial skeleton might play in investigations of anemia (e.g., Smith-Guzmán, 2015; Gomes et al., 2021; Mangas-Carrasco and López-Costas, 2021; Schats, 2021).

Diagnosis of specific conditions plays a crucial role in reconstructing health and life histories in past communities, providing long-term perspectives on current public health problems. At a basic level, Mays (2018:13) identified four conceptual frameworks used in paleopathological diagnosis: "1 The comparative approach, 2 The biological approach, 3 Direct measurement of a diagnostic parameter, 4 Direct identification of the causative microorganism (for infectious disease)". As Mays (2018) discussed, paleopathologists have focused on the first two approaches. However, in the case of anemia, the nature of clinical diagnosis based on hematologic and biochemical parameters means paleopathologists have lacked a solid basis for the comparative approach (see Section 3). Reliance on porotic lesions should be reconsidered.

In this paper it is argued that confounding factors to diagnosing anemia have been created by the omnipresent nature of porous lesions across the spectrum of pathological conditions and the absence of such lesions in many cases of anemia. The failure to recognize the differences in clinical versus paleopathological work, use of recording systems that lack a basis in biological processes, and little consideration of the life course approach in lesion evaluation have compounded the problems. The thesis proposed in this paper is that acquired anemia would be better approached via direct measurements of changes in bone caused by marrow expansion (hyperplasia – a condition that arises in anemia), supplemented by careful evaluation of any linked lesions. Dealing with diagnosis issues will necessitate a considerable investment in time and resources to develop a fundamentally different approach to evaluating anemia. While not quick or easy, this paper's suggestions on ways forward are achievable. There have been many recent positive developments in theoretical and practical approaches to diagnosing conditions and developing datasets and methodologies that would facilitate the successful adoption of new approaches over the next ten years. The proposed shift would enable greater confidence in diagnosing acquired anemia and facilitate getting the most from longer-term perspectives on this important condition.

2. Proposed shift in approach to the diagnosis of anemia

While porotic lesions can occur in cases of anemia, multiple factors will lead to spurious or misleading results if it is simply assumed that porotic lesions equate to anemia with no thought given to the variables involved. These confounding factors likely underlie the extensive debates and lack of consensus amongst paleopathologists whose focus in considering anemia has been porotic lesions. An analogy to the current situation with anemia in paleopathology would be the confounding results that would be produced if researchers tried to investigate osteoporosis using just the presence of fractures as indicators of the condition. Although fragility fractures occur in osteoporosis, fractures occur for many other reasons. Accounting for the age-related nature of bone development and loss, and adopting a biological approach when evaluating fragility fractures prevents debates about whether fractures are linked to osteoporosis. More is learned about osteoporosis in past groups with consideration of the age-related nature of fractures and their tendency to occur at skeletal sites with high trabecular content. However, to understand the issues of age-related bone loss and osteoporosis experienced in past groups, bone quality and quantity are used as primary measures of bone loss and osteoporosis, with highly focused fracture data providing additional information on the lived experience of past community members (see Curate, 2014; Ives et al., 2017; Macintosh et al., 2017; Agarwal, 2018; Brickley et al., 2020: Chapter 6; Agarwal, 2021; Miszkiewicz et al., 2021; van Spelde et al., 2021). Acquired anemia is better considered as a condition primarily diagnosed via direct measurement of a diagnostic parameter (i.e. changes in bone initiated by marrow hyperplasia) that can be supplemented with carefully considered information on porotic and other lesions.

3. Diagnosing anemia in clinical medicine, a brief review

Anemia is a condition in which oxygen transported to tissues is reduced to a level that no longer meets the physiological need, and the patient's signs and symptoms are non-specific, even in marked cases. The third diagnostic approach listed by Mays (2018:13), "direct measure of a diagnostic parameter" is used in the clinical diagnosis of acquired anemia; anemia is defined by hemoglobin levels alone with other biomarkers used to ascertain the underlying cause and arrive at a targeted course of treatment. Red blood cells (RBCs) which contain hemoglobin, a protein which facilitates oxygen transportation to tissues, are measured. Determining RBC mass is complex and time-consuming, so the measures typically used to assess and interpret the quantity of RBCs require caution. Various factors affect the concentration of RBCs in plasma; for example RBC concentration will be increased by dehydration and can be decreased by raised plasma volume during pregnancy (Maakaron, 2021). Typically hemoglobin concentration (Hb) is measured and is often assessed alongside RBC count and hematocrit (Hct) against established cut-offs for populations based on factors such as age, sex and pregnancy (World Health Organisation, 2004; Brown, 1991; World Health Organization, 2011; Maakaron, 2021). Maakaron (2001) draws an analogy with fever, pointing out that mild cases will often escape the attention of clinicians, and investigation of this sign is required to determine the underlying cause. Bone marrow biopsy, alongside other hematologic and biochemical parameters, may be used as aids in determining the underlying cause of anemia (Hoffmann et al., 2015). Lesions of bone play no role in making a clinical diagnosis, but the hair-on-end sign is considered a pathognomonic indicator of childhood anemia (see Section 5.1.2).

In many current societies with highly developed health systems, anemia in aging populations is a common issue (Balducci, 2003; Gaskell et al., 2008). While, as set out in Section 5.2, marrow hyperplasia can develop in older adults with anemia, a notable section of this demographic have mild anemia, often resulting from underproduction or slight decrease in survival of RBCs linked to anemia of chronic disease/inflammation (Weiss et al., 2019; Brickley et al., 2020:202). A much rarer demographic is those who experience myeloproliferative disorders, many of which are associated with marrow hyperplasia (Steer et al., 2017). Readers should also be aware that some rare forms of anemia develop in cases of marrow hypoplasia or aplasia; these conditions are rare and still poorly understood, but from evidence currently available, it is evident such conditions, which now have high mortality, will have been rarer in past groups (see Chen, 2005; Young, 2006: Brickley et al., 2020:211).

4. Diagnosing anemia in paleopathology, a brief history

Beyond the binary margins of paleopathology at which porotic lesions either are or are not caused by anemia (Section 1), when writing about the condition, most of those currently working in paleopathology display hesitation and include caveats. Often researchers mention that multiple conditions can cause porotic lesions, and many have settled into using CO and/or PH as an indicator of poor health, often with mention of the potential for co-occurring disease (e.g., Novak et al., 2017; Fernández-Crespo et al., 2018; Fujita and Nishizawa, 2022). The need for microscopic examination for greater certainty when assessing porotic lesions is often mentioned (e.g., Williamson, 2015; Thompson et al., 2022). However, all approaches to anemia based on assessing porotic lesions miss the fundamental problem of relying on lesions (see Section 2). To evaluate how this situation arose, it is necessary to briefly review the extensive history of work on porotic lesions and anemia in paleopathology.

Early paleopathologists with a background in medicine, such as Williams (1929) and Jarcho and colleagues (1965), used the term symmetrical osteoporosis to describe porotic cranial lesions with hypertrophy of the diploë in potential cases of anemia. There were also reports of such lesions being discovered during autopsy in contemporary individuals (Müller, 1935). Larry Angel introduced the term 'porotic hyperostosis' to refer to all such cranial lesions while working on skeletal material in the Eastern Mediterranean, a region with thalassemia (Buikstra and Prevedorou, 2012). Nevertheless, others opted for CO in their discussion of the etiology of orbital lesions (see Hengen, 1971). As discussed in several reviews (e.g., Buikstra and Prevedorou, 2012; Mays, 2012; Ortner, 2012), Angel specifically considered anemia diagnosis via evidence of bone changes that likely developed in response to marrow hyperplasia. However, he recognized that many conditions contribute to porotic lesion formation. In a discussion of work on such cranial lesions Ortner pointed out that Angel was aware that conditions other than anemia cause porotic lesions to develop "several skeletal disorders that stimulate this abnormality including anemia, infection, cancer, scurvy and rickets" (Ortner, 2012:251). Buikstra and Prevedorou (2012) highlight various other aspects of Angel's work that anticipate later discussion in paleopathology, such as issues later termed the 'osteological paradox' (Wood et al., 1992). Angel's work also contained "careful observation of the morphology and location of the lesions encountered in skeletal remains, coupled with a detailed reading of the biomedical literature while paying close attention to relationships between hard and soft tissue anatomical structures at the sites in the skeleton where lesions were characteristically seen" (Mays, 2018:16); key elements that later became known as the 'biological approach'. Another approach now considered best practice was Angel's evaluation of lesions throughout the skeleton in making a diagnosis (Buikstra and Prevedorou, 2012; Klaus, 2017; Mays, 2020). Angel worked in a region with genetic forms of anemia, thalassemia, and sickle-cell anemia. However, as paleopathologists began considering anemia in regions of the world where most cases would be acquired anemia, many of the key elements that defined early anemia research were lost.

Hindsight makes the change, described by (Mays, 2012:292), as a shift in focus from the 'hyperostosis' - the changes in marrow, to an emphasis on the 'porotic' aspect of lesions, seem obvious, but it was a gradual process. The shift likely arose because porotic lesions are readily identified and require no complex equipment to score (Mays, 2012). Grauer and Ortner (2019) made similar points and postulated that introducing the scoring system for porotic cranial lesions in the Handbook edited by Buikstra and Ubelaker (1994) unintentionally cemented this position resulting in many authors equating description with diagnosis. The fact that clinical diagnosis of anemia, particularly acquired forms of the condition, relies on a direct measure of a diagnostic parameter based in hematology (Section 3) compounds these problems. However, many North American scientists started to assume that porotic cranial lesions (CO and PH) were caused by anemia, especially iron deficiency anemia (IDA), and the two became synonymous (e.g., El Najjar et al., 1976; Taylor, 1985; Ubelaker, 1992; Stuart-Macadam, 1987, 1992). Despite inherent difficulties in comparing disease in current groups to data obtained from paleopathology (e.g., see Mays, 2020; Appleby, 2023), interesting insights were produced from comparisons of data on levels of acquired anemia diagnosed using clinical hematologic parameters with paleopathological data on porotic cranial lesions from archaeological sites in Guatemala (Wright and Chew, 1998). Although 30% of the tested contemporary Guatemalan populations were clinically classified as having anemia, no Guatemalan radiologists reported observing radiological signs of anemia in their clinics (Wright and Chew, 1998:931).

In the earlier 2000s, with increased paleopathology research on specific conditions, particularly in metabolic diseases, the omnipresent nature of porotic lesions was recognized and accompanied by a shift toward recognition that conditions other than anemia might underlie such lesions (e.g., Ortner, 2003:102–4; Klaus and Tam, 2009; Cole and Waldron, (2019); Brickley et al., 2020:35–38; Perry and Edwards, 2021). Wapler and colleagues undertook seminal work that directly compared the macroscopic evaluation of porotic lesions of the orbital roof (aka, CO) with underlying bone structures and considered possible pathological and physiological contributions to lesions (Wapler et al., 2004). These researchers (*ibid.*) demonstrated multiple reasons for porotic lesions other than marrow hyperplasia. Although they considered the potential contribution to lesion formation of age-related bone loss and osteoporosis, there was no direct consideration of the life-course or possible age-related natures of lesion formation in the adults examined. The key findings in Wapler et al. (2004) paper have largely been overlooked. For example, soon after this study, and still taking the stance that porotic cranial lesions were indicative of anemia, Walker and colleagues questioned whether IDA was the causative mechanism, arguing that physiological changes to bone in response to IDA would not cause porotic lesions (Walker et al., 2009). However, both Oxenham and Cavill (2010) and Mays (2012) use both clinical data and discussion of physiological processes to challenge this position (though see recent discussion of mechanistic issues by Schats, 2023). Despite providing detailed information on the multiple conditions that might cause porotic cranial lesions Walker and colleagues take one cause, IDA, and swap it for a second, nutritional megaloblastic anemia. This problematic swap is not explicitly discussed in the debate on the Walker team's work. There is no 'single cause' of porotic lesions, and it cannot be assumed that a commonly occurring condition in a community will automatically underlie all such lesions observed.

Reviewing the situation and developments in 2012, Ortner concluded that researchers should take what has since been termed 'a biological approach' (see Mays, 2018, who discussed how aspects of the framework would apply to anemia). Nevertheless, the thin evidence for macroscopically visible skeletal lesions in acquired anemia is the bottom line; it will be a limiting factor for any paleopathological study focusing on lesions as a basis for diagnosing anemia. To advance, this fundamental problem must be acknowledged.

Recent developments have moved beyond the direct sectioning employed by Wapler et al. (2004) and opened non-destructive techniques for evaluating bone microstructures (see Conlogue et al., 2020). Early small-scale studies using computed tomography (CT) raised interesting questions (see Saint-Martin et al., 2015; Rivera and Mirazón Lahr, 2017) and aspects of these studies and ways forward are discussed in Section 5. However, the most recent widespread shift has seen researchers use CO and PH as non-specific indicators of poor health in studies of sufficiently large scale to overcome some of the problems of the 'noise' created by multiple potential causes of porotic lesions. For example, using a sample of 1702 individuals from the Netherlands, Schats (2022) convincingly mapped known patterns of CO and malaria, a condition, when long-standing, that invariably results in anemia (Brickley et al., 2020: 202–8; Schats, 2023). Another example is the spatial paleopathological meta-analysis of Andean data on CO from

5760 skeletal individuals undertaken by Scaffidi (2020). Environmental factors such as hyper-aridity and seasonal variability in freshwater supply were the strongest predictors of CO, explaining a third of variability in frequency, confirming that climate and water availability influenced risks to health in these past communities. Cultural or short-term environmental stressors explained the other two-thirds. Finally, many researchers now consider porotic lesions as a stress indicator; they have been successfully integrated into work taking a syndemic approach to conditions that have the potential to produce such lesions (see Perry and Gowland, 2022).

There is good evidence that most acquired forms of anemia have the potential to produce detectable evidence of marrow hyperplasia in bone. Exceptions include some cases of anemia of chronic disease/inflammation, particularly in elderly individuals, and the rare cases of anemia in which there is no bone marrow response (see Section 3). However, as histological data on cell type, alongside other parameters, are required to determine the cause of acquired anemia (Section 3; Ragsdale and Lehmer, 2012), paleopathologists will be doing well to suggest a case of acquired anemia confidently and should avoid overdiagnosis.

5. Discussion and ways forward

The proposed approach, with adoption of direct measures of diagnostic parameters supplemented by a combination of the biological and comparative approaches to potential lesions, would mark a fundamental change in the diagnosis of anemia. If accepted and applied, it would enable paleopathologists to make significant progress in considering anemia in past communities. This paper focuses on acquired anemia but forms a basis for work on congenital conditions causing anemia such as sickle-cell disease and thalassemia (see Hershkovitz et al., 1997; Lewis, 2012; Brickley et al. 2020: Chapter 9; Panzer et al., 2023).

5.1. Ways forward: better use of lesions and integration of biological approach

Skeletal lesions will develop in some individuals with acquired anemia, like fractures in those with age-related bone loss and osteoporosis. While use of measurable features is proposed as a basis for suggesting cases of acquired anemia in archaeological human remains, obtaining data that forms the foundation for such an approach will be a longer-term collective effort involving collaborative research with clinicians and biomedical professionals working on contemporary health issues (see Section 5.3). Consideration of lesions will likely continue at some level, both with and without metric and/or radiographic evaluation, but porotic lesions will have a limited place in firm diagnoses when used in isolation or in small-scale studies. Where making a specific diagnosis of anemia is the aim and lesions are considered, paleopathologists must use them better and step back to the 'biological' approach used by Larry Angel (e.g., Angel and Thomas, 1967).

In paleopathology, skeletal evidence of marrow hyperplasia must serve as the 'gold standard' for diagnosing anemia. Table 1 sets out broad comparisons between radiological imaging methods for evaluating skeletal features associated with marrow hyperplasia in the cranium. Using a combination of comparative clinical information supported by a biological approach, the table is arranged according to diagnostic certainty currently ascribed to features. Recommendations made in Table 1 are covered in more detail in the following discussion, alongside suggestions on approaches to the post-cranial skeleton. A working group on protocols for radiological evaluation of porotic cranial lesions arising from the Workshop on Porotic Cranial Lesions, organized by Dr. Santos in Coimbra, Portugal, in July 2023, is developing protocols for use in paleopathology, and it is anticipated these will be available shortly.

5.1.1. Use of the hair-on-end radiographic appearance

The hair-on-end radiographic appearance (also referred to as a 'radial appearance' and/or 'vertical' or 'trabecular striations' in some

Table 1
Comparison of X-ray and Micro-CT evaluation of cranial features associated with marrow hyperplasia in acquired anemia.

	Feature	Location	Assessment method	Evaluation	Notes
1	Hair-on-end appearance	Typically frontal or parietal	Observational	Standard x-ray either film or digital.	Care required with positioning of bone and consideration of full range of conditions that result in cranial vault thickening and changes in radiographic texture (see Section 5.1.2). Feature results from projecting three-dimensional features onto a 2D image, so single-slice micro-CT or microscopy cannot be used.
2	Ratio of diploic to cortical bone	Various	Metric	Standard x-ray either film or digital, microscopy (histomorphology) or micro-CT evaluation	See Table 3 for suggested measurements and Section 5.3 for primary recommendations on techniques used for evaluation. Preliminary information on anticipated ratios of those with/without anemia is currently only established for the frontal and parietal.
3	Widened diploic space	All regions	Observational & Metric	Standard x-ray either film or digital, CT, microscopy or micro-CT evaluation	While this feature may be suspected from observations, metric evaluation is required to suggest a diagnosis. See Section 5.3 for primary recommendations on techniques used for evaluation and reporting results.
4	Cortical thinning/ Loss of outer table	Typically frontal or parietal	Observational & Metric	Observation cannot be used in isolation for diagnosis, but may prompt the need for metric evaluation using standard x-ray either film or digital, microscopy or micro-CT.	Occurs in multiple conditions. Metric data and evaluation of the exact patterns of thinning and links to other structural changes throughout the skeleton are important for suggesting a diagnosis. See Section 5.3 for primary recommendations on techniques used for evaluation and reporting results.
5	Granularity and textural changes	Cranial vault	Observational	Standard x-ray either film or digital.	Occurs in multiple conditions. Should only be used as a prompt to consider other investigative approaches. Feature results from projecting three-dimensional features onto a 2D image, so care is required using single-slice micro-CT or microscopy.

Note: Numerical order of features relates to level of diagnostic certainty based on currently available data.

earlier clinical work, see Aksoy et al., 1966; Sebes and Diggs, 1979) has primarily been discussed clinically with genetic anemias, but has also been reported in cases of acquired anemia (e.g., Eng, 1958; Agarwal et al., 1970; Weerakkody et al., 2020). For a discussion of the mechanisms behind such structural changes, see Brickley et al. (2020:220–24).

Unambiguous hair-on-end lesions could be considered pathognomonic for anemia as the lesion occurs in response to marrow hyperplasia; care is required to exclude lesions that arise due to rapid bone formation of bone spicules. Such lesions have been reported in some neoplastic conditions using terms such as 'sunburst' (e.g., Bloom et al., 1987). Reynolds (1965:78), discussing clinical diagnosis, highlights that care is required to differentiate "false" hair-on-end appearance that can be associated with normal sagittal sutures; in such cases, fissuring and irregularity, which can be confused with a striated appearance, are limited to the periphery of the vault rather than extending through the entire thickness. In paleopathology, the hair-on-end appearance often needs to be confirmed, even on direct evaluation of broken or cut surfaces, as illustrated by the comparison of a cut section and radiograph of cranial bone in Fig. 1. Radiography is now widely available and can be applied to fragments of bone, making it ideal for assessing archaeological human bone. However, despite the wide availability of radiographic equipment, hair-on-end lesions are no longer routinely considered in paleopathological research on anemia. Indeed, there are several reports of hair-on-end appearance where no radiograph was presented or discussed; instead, these are cases with cranial thickening accompanied by a porotic external appearance (e.g., Ubelaker, 1992; Viva et al., 2021). Such lesions occur in multiple conditions that lead to either primary or secondary inflammatory processes of the bone (Schultz, 2003:102) and other metabolic diseases (Brickley et al., 2020:214–216). A few older paleopathological reports use radiography to evaluate the hair-on-end appearance (e.g., Zaino, 1964; El-Najjar and Robertson, 1976; Stuart--Macadam, 1987) and we should return to this practice. Paleopathologists must value the information derived through paleopathological assessment of human remains and actively evaluate and report hair-on-end lesions. However, their absence does not mean an individual did not experience anemia (see Reynolds, 1965; Agarwal et al., 1970).

5.1.2. *Porotic lesions*

In the extensive debates on anemia and porotic lesions in paleopathology, a critical fact omitted from the discussion is that there will be no porotic skeletal lesions in many cases of acquired anemia, and those that develop are of no interest to clinicians and are unlikely to feature in their work. Various attempts have been made to sort out the problems of diagnosing anemia, but these have focused on recording systems based on the macroscopic appearance of porotic lesions (e.g., Nathan and Haas, 1966; Stuart-Macadam, 1985; Rinaldo et al., 2019). Consistently recording lesions will have limited value if divorced from understanding the biological mechanisms underlying lesion formation. Biehler-Gomez et al. (2020) demonstrated that problems arise when researchers cannot identify the underlying biological processes in recorded lesions and differentiate between lesions of varied biological origins.

The paper by Wapler et al. (2004) took what is now described as a 'biological approach' (see Mays, 2018); they examined the underlying mechanisms behind the formation of porotic lesions in the orbital roof. Evidence for marrow hyperplasia was present in less than half of adults with CO in a sample of archaeological individuals from the Sudan; they omitted the evaluation of marrow hyperplasia in individuals without porotic lesions. Widened marrow spaces arising from reduced trabecular structures and thinning and perforation of the orbital plate were taken as evidence of marrow hyperplasia and hence anemia in 20/85 individuals, with a lower degree of diagnostic certainty in 17 cases. More recently, some of this team evaluated the potential to use non-destructive imaging techniques to provide equivalent information (Saint-Martin et al., 2015). Based on the evaluation of the small sample of $n = 7$ orbital roofs from five individuals still undergoing growth and development, these authors concluded that the external appearance did not reflect the underlying bone processes. Although evaluating changes in the diploë would be impossible in most cases, with care basic biological processes are discernable for lesions involving the cortical surface.

Both adults and those still undergoing growth and development were scanned in a small study of Dutch archaeological individuals with $n = 7$ and without $n = 2$ porotic orbital lesions in a recent study using micro-CT by Schats and colleagues (2022). Here, considerable care was taken to select individuals with lesions with the highest chance of having bone changes likely linked to marrow hyperplasia. All those with lesions showed features of the trabecular architecture interpreted as evidence of marrow hyperplasia. Neither of those without lesions had clear evidence of marrow hyperplasia with visual assessment. None of those evaluated by Schats and colleagues (2022) had periosteal reactions (which can also have a porous appearance). Cases with such lesions were also excluded by McFadden and Oxenham (2020), who used CO as a general indicator of malnutrition. Like many other researchers they assumed that periosteal reactions and bone deposition would not be part of anemia. However, 'mixed lesions' in which subperiosteal new bone formation develops at sites of porotic lesions are possible in anemia (see the review of clinical cases by Brickley et al., 2020:214) as well as conditions that cause an inflammatory reaction such as infection and scurvy (see Brickley and Mays, 2019).

The underlying reasons why lesions with a porous appearance develop are varied (see Brickley et al., 2020:35–38; Brickley and Morgan, 2023), but the framework provided by the biological approach has proved helpful in enabling paleopathologists to tackle this difficulty. Factors to consider in using porous lesions of the orbital roof and cranial vault to contribute to suggesting a diagnosis are covered in Fig. 2. This Figure highlights that anemia does not always produce porotic lesions at the bone surface. Considerable further work is required to determine what aspects of porotic lesions are worth recording to evaluate anemia. The full spectrum of lesion expression must be included alongside those with no externally visible lesions and individuals who died at a range of ages, taking a transparent life-course approach to consider lesions (Section 5.2). As has been shown by various authors (e.g., Wapler et al., 2004; Saint-Martin, 2015), porous cranial lesions can be linked to

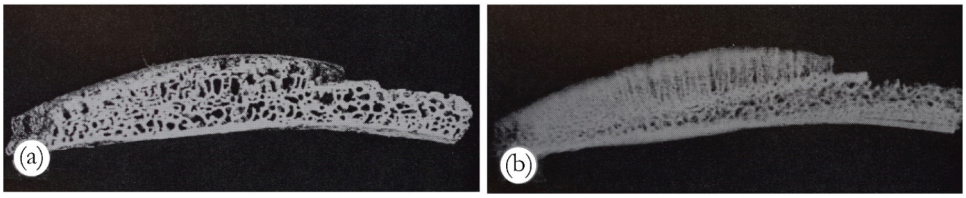

Fig. 1. (a) Photograph of a slice of bone from a macerated calvarium, and (b) roentgenograph of a skull excavated in New Mexico, 1000-1100 AD, showing "hair-on-end" feature. Jaffe interpreted these lesions as the effects of some type of haemolytic anemia. This is strikingly demonstrated in (b). It is clear that this appearance is created by osseous trabeculae, which were deposited by the pericranium on the outer table. These trabeculae are directed more or less at right angles to the surface of the calvarium. See Jarcho et al. (1965) for further details. Reprinted from Jaffe (1972) *Metabolic Degenerative and Inflammatory Diseases of Bones and Joints.* Philadelphia: Lea and Febiger. Fig. 181. The Creative Commons license does not apply to this content. Use of the material in any format is prohibited without written permission from the publisher, Wolters Kluwer Health, Inc. Please contact permissions@lww.com for further information.

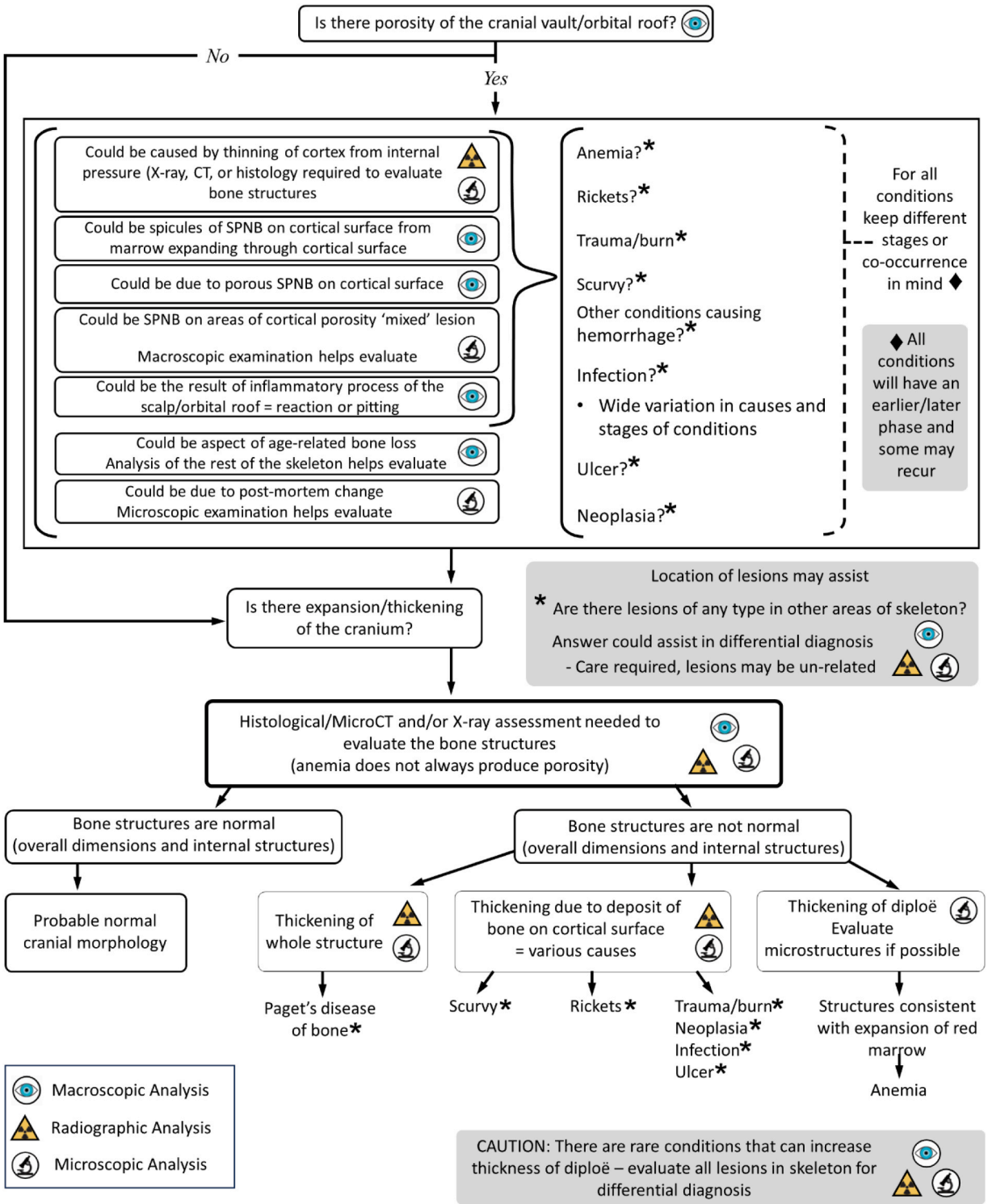

Fig. 2. Porous lesions of the orbital roof and cranial vault: flow diagram of factors to consider in suggesting a diagnosis. Reprinted with minor modification from Brickley et al. (2020). *The Bioarchaeology of Metabolic Bone Disease, Second Edition*. Academic Press: San Diego, Page 216, Fig. 9.5, Copyright (2020), with permission from Elsevier. See Chapters 4, 5 and 8 for further information on the other pathological conditions mentioned.

underlying bone structures typical of marrow hyperplasia in some individuals, but without metric evaluation to confirm which individuals have evidence for marrow hyperplasia, there is considerable potential for error. Errors will occur when individuals with marrow hyperplasia exhibit no porotic lesions and when porotic lesions are present, but not linked to underlying marrow hyperplasia; we do not currently know how context-dependent error rates are.

Although visual assessment of broken bone can be used at the individual level to suggest whether surface porotic lesions might be linked to underlying changes linked to marrow hyperplasia (see Brickley et al., 2020:215), at the community level, such an approach will be inadequate as post-depositional damage is too random to allow consistent evaluation. Work to date has focused on the orbital region of the frontal bone. While the region behind the orbital plate is challenging to evaluate and

visualize in clinical work (Brickley, 2018), the factors of low biomechanical remodeling discussed by McFadden and Oxenham (2020) may make this region particularly valuable. The potential value lies in the fact that during growth and development this is a key site of available erythropoietic tissue, and hence potential structural changes linked to marrow hyperplasia. However, biomechanical necessity is not the predominant factor influencing structural properties.

To better understand links between porotic lesions (or their absence) in anemia, work on microstructural changes in response to normal development and marrow hyperplasia needs to be developed for the entire skeleton in individuals of a range of ages. Biological factors such as cortical thickness and associated soft tissue structures that may influence lesion development must be considered, alongside technical issues relating to investigative methodologies employed (e.g., see Anderson et al., 2021). As shown in the schematic representation of a generic bone in Fig. 3, cortical thickness will be a factor in lesion development. Data on the prevalence of porotic lesions that are clearly linked to bone changes associated with marrow hyperplasia need to be evaluated for both the cranial and post-cranial skeleton of individuals who died at various stages of life from multiple contexts. Porosity will have been present in those with hair-on-end appearance and "dissolution" of the outer table in a small number of cases of sickle cell disease noted by Reynolds (1965:72). The unknown is what proportion of the numerous individuals simply reported as having atrophy or thinning of cranial or post-cranial bones (Burko et al., 1961; Agarwal et al., 1970) will exhibit porous skeletal lesions. As pointed out by Anderson et al. (2021) systematic investigation of clinical computed tomography is needed to ascertain the prevalence of porotic lesions in contemporary populations; this work should be conducted collaboratively with partnerships of paleopathologists and contemporary clinicians/biomedical researchers. Gathering the required information will be an iterative process as paleopathologists move from clear-cut, severely altered examples to full integration of those with less marked microstructural skeletal changes.

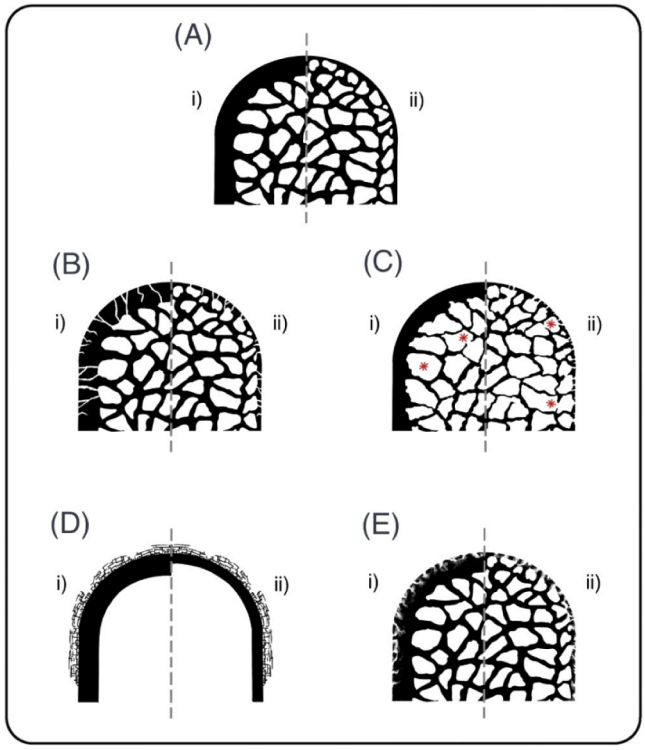

Fig. 3. Generic bone with varying cortical thicknesses illustrating basic principles underlying lesion formation occurring in the four basic biological mechanisms that results in porotic lesions. Thick (i) and thin (ii) cortical bone are shown for each. Cortical thickness is a key determinant of lesion appearance and morphology. Idealized versions of the lesions caused by each mechanism are shown, but preservation, taphonomic variables, and presence of multiple conditions can all affect their appearance. (a) Normal bone. (b) Porosity due to a vascular inflammatory response. (c) Porosity due to marrow hyperplasia. Star = enlarged spaces in bone occupied by marrow. (d) Porosity due to deposition of porous sub-periosteal new bone (formed as a response in many conditions/circumstances). (e) Porosity due to impaired mineralization Reprinted from Brickley & Morgan (2023) Metabolic and Endocrine Diseases. In Grauer (Ed.), *The Routledge Handbook of Paleopathology*. Routledge: London. Fig. 19.1, page 348. Reproduced with permission from Taylor & Francis Group.

5.2. *Ways forward: adopting a life-course approach*

What paleopathologists see is the product of accumulated aspects of an individual's life (see Grauer, 2018). Nonetheless, there can be a tendency to work as if all lesions recorded in skeletons are contemporaneous. The amount of bone built, and potential porotic lesion development will depend on multiple factors from the in-utero environment onwards (see Halcrow and Gowland, 2020). In-utero and post-partum events, genetics, nutrition, activity, and health have a closely interrelated relationship in determining bone developed and potentially lost with age and in the face of health issues. These may be multiple and recurrent, and everyone will be different (see recent discussion in O'Donnell et al., 2023).

Although, anemia is especially common in younger women and children, the condition is relevant to everyone at all stages of life. The production of red blood cells (erythropoiesis) by marrow is initiated during fetal development (~11–12 weeks post-conception) and continues throughout life (Charbord et al., 1996; Baron et al., 2012; Neoh et al., 2022). Those with anemia who cannot meet the physiological need for oxygen from available marrow will normally experience marrow hyperplasia. Beyond the earliest stages of infancy, where red (hemopoietic) marrow is present throughout the skeleton, marrow hyperplasia may potentially involve the expansion of existing red marrow and/or reconversion of mixed marrow to a hemopoietic state. Exact patterns will depend on age of onset of demand for increased RBC production and prior individual history (Yasuda et al., 2016; Brickley, 2018; Brickley et al., 2020:210). Pressure erosion from marrow hyperplasia has the potential to result in porotic lesions of the cortical bone surface, but there should be active consideration of the possibility that porotic lesions at different skeletal regions may have different underlying causes. While paleopathologists observe the status of a condition as it is at death, more active consideration of the life-course approach and active engagement with data on average patterns of marrow development and change throughout the skeleton would enable researchers to gain more from paleopathological data.

In paleopathology it is recommended that the age at death is considered alongside distribution of the presence and absence of evidence for marrow hyperplasia. These pieces of information need to be evaluated alongside information on the normal patterns of conversion of red to yellow marrow throughout the skeleton. Using data from multiple published studies Brickley (2018) set out broad age-related changes in red, mixed and yellow marrow across the skeleton (see Fig. 4). While marrow is red it has the potential to respond to the need for compensatory hyperplasia that can arise in anemia. Evidence reviewed indicates that mixed marrow also has the potential to re-convert to red but with age marrow reaches a point where this will no longer occur (Brickley, 2018: 899). It is likely that in those with longer-term chronic anemia may maintain erythropoietic tissue longer than might be anticipated, so when discussing cases in paleopathology it is best to discuss the age of initiation of changes.

To date most work in clinical medicine and paleopathology has focused on the cranial bones. Average patterns of marrow development mean that in all but the most severe cases of anemia, initiation of any linked porotic lesions has the potential to occur later in the cranial vault than the orbit (Brickley, 2018). Age-related patterns in likely lesions

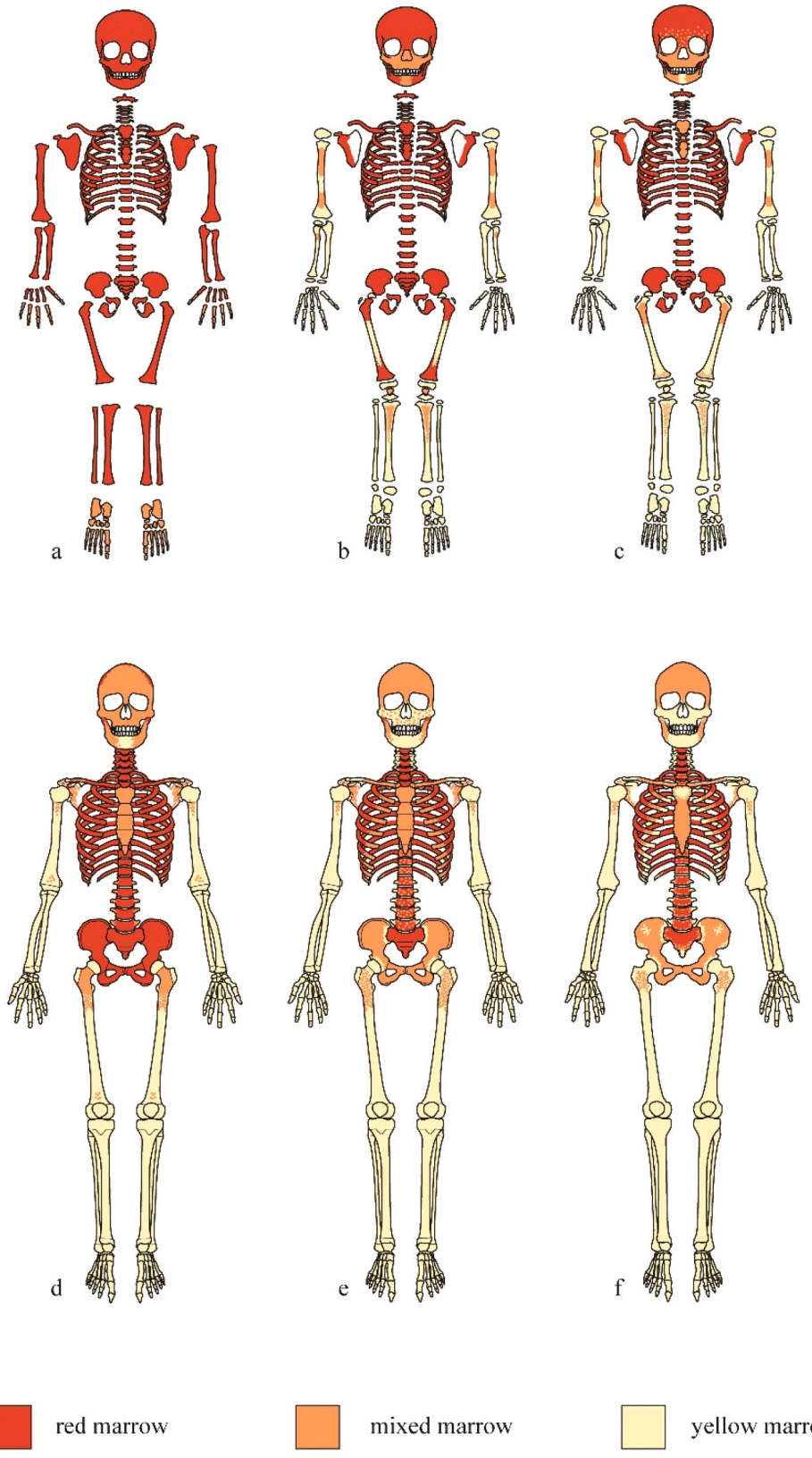

Fig. 4. Broad patterns in the distribution of red, mixed and yellow marrow from birth to 25 years +. a. <1 year, b. 1-5 years, c. 6-10 years, d. 11-15 years, e. 16-25 years, f. 25+ years. There are slight inconsistencies in published data and sources acknowledge individual variation within the average pattern seen. Data for the compilation of the figure was drawn from the following sources: Custer (1974), Dawson et al. (1992), Kaneda et al. (1996), Kricun (1985), Małkiewicz and Dziedzic (2012), Mirowitz (1993), Moore and Dawson (1990), Ricci et al. (1990), Simonson and Kao, 1992, Taccone et al. (1995), Vahlensieck et al., (1995), Vahlensieck and Layer (2016). Vande Berg et al., (1998), Waitches et al., 1994, Yamada et al. (1995), Zawin and Jaramillo (1992). Reproduced from Brickley (2018) Cribra orbitalia and porotic hyperostosis: A biological approach to diagnosis. *American Journal of Physical Anthropology* 167:896-902. Fig. 1, with permission from John Wiley & Sons.

formation for the orbit were apparent in the study by McFadden and Oxenham (2020) using 37 collections of 100 + individuals meeting their inclusion criteria taken from the Global History of Health project (Steckel and Rose, 2002; Steckel et al., 2018), backing up the findings of previous researchers (e.g., Williams, 1929; Stuart-Macadam, 1985). There are clinical cases of acquired anemia with cranial changes in infants and younger children, many of whom come to medical attention having been born pre-term (e.g., Shahidi and Diamond, 1960; Burko et al., 1961). However, there are also quite a number of reported cases of cranial vault thickening and related changes in cases of anemia, in older individuals, often aged 12 years plus (e.g., Eng, 1958; Aksoy et al., 1966). Reviewing radiological changes apparent in the cranial bones of those with a genetic form of anemia (so present since birth) the study by Sebes and Diggs, (1979) reported that although changes such as diploic expansion can be present at young ages (< 2 years), such changes appear to be broadly progressive in the first three decades of life, with expansion in the frontal bone occurring prior to the parietal (Sebes and Diggs, 1979). It is clear from their discussion of clinical reports that systematic studies and consistent diagnostic standards are lacking. From data available in the recent study by O'Donnell and colleagues (2023), it is impossible to be sure if evidence of marrow hyperplasia in the cranial vault occurs later than the orbital roof and increases with age; the available data stop at 15 years. However, seeing the pattern found in a more extensive or age-extended study would be interesting.

Although unlikely, evidence of marrow hyperplasia may be found in the parietal but not the bone underlying the orbital region of the frontal bone. There is, however, far more potential that an individual's circumstances may have changed, and no evidence for marrow hyperplasia will be present in the frontal bone, but it would be detectable in the sternum. As illustrated in Fig. 4, there is considerable potential from studies that take in the entire skeleton (see Klaus, 2017; Mays, 2020) using techniques such as micro-CT with radiation doses beyond what can be used in clinical studies. Some clinicians have recognized the limitations of studies of acquired cases of anemia that focus on cranial bones, but understandably, few attempts have been made to compare radiographic findings across the skeleton (but see Aksoy et al., 1966). A life course approach will assist in working out potential links between cranial and post-cranial skeletal lesions and patterns of skeletal changes linked to anemia at all life-course stages. Information in Table 2 is designed to assist researchers in developing hypotheses on the distribution and pattern of skeletal changes associated with marrow hyperplasia that can be tested in collaborative projects with contemporary clinicians and using findings from paleopathological investigations. The metric data sets discussed in Section 5.3 will be critical and enable paleopathologists to get past just considering porotic lesions and better consider the evidence for marrow hyperplasia in past groups.

In some previous paleopathological work, researchers have made statements on whether porotic lesions of the orbital roof and cranial vault have the same underlying cause, but only analyzed those with one of these lesion types (e.g., Rivera and Mirazón Lahr, 2017). From an analysis of the extensive datasets on CO and PH gathered by Weckler in the 1800s using Bayes' theorem, Cole and Waldron (2019) concluded that there is no evidence that the two are causally related. However, age differences were not engaged with. Similarly, various studies of archaeological bone that considered both cranial and post-cranial lesions also failed to find correlations between porotic lesions in different regions of the skeleton (e.g., Djuric et al., 2008; Schats, 2021; Gomes et al., 2022), but in these cases, potential differences in age of initiation of lesions were not factored into the discussion. To move forward, paleopathologists need to engage with a life-course approach actively.

5.3. *Ways forward: start to develop metric data sets*

Those working with skeletal material have long appreciated that patterns of growth and development are critical for understanding aspects of health conditions and disease in past communities (e.g., Garn, 1981; Humphreys, 1998; Saunders, 2007). Quantitative shape analyses have been widely used in palaeopathology to describe and diagnose conditions (see Gilmour and Plomp, 2022). However, despite early use in considering diagnosis of anemia (e.g., Angel, 1966; Stuart-Macadam, 1987) in paleopathology, metric evaluation has been largely abandoned in recent years by those considering porotic lesions as indicators of anemia. The primary use of metric data sets in paleopathology has been in assessing age-related bone loss and osteoporosis. Individuals affected by anemia will likely have less bone than expected; pressure erosion resulting from marrow hyperplasia can potentially affect both cortical and trabecular bone structures associated with marrow throughout the skeleton (Section 5.1). Nevertheless, currently, no widely accepted reference data exist on skeletal structures such as medullary cavity dimensions and trabecular microarchitecture. Hence, paleopathologists lack a metric basis for suggesting many potential alterations due to marrow hyperplasia that could be used to suggest a diagnosis of anemia. Collaborative work with clinicians and those in biomedical facilities will be important to gather some of the additional data needed to better understand some of the biological information on the relationship between anemia and skeletal changes and enable paleopathologists to

Table 2
Potential development and maintenance of bone changes linked to hyperplasia of hematopoietic marrow across the post-cranial skeleton.

	<1 year	1–5 years	6–10 years	11–15 years	16–25 years	>25 years	Notes
Skeletal region							
Hand phalanges	+	-	-	-	-	-	
Metacarpals	++	-	-	-	-	-	
Proximal humerus	++	+	+/-	-	-	-	Differences between the proximal humerus and femur are minimal and some authors plot these regions together (e.g.,Vande Berg et al., 1998)
Proximal femur	++	++	+	+/-	-	-	
Manubrium	++	++	+	+	+	+/-	
Sternum	++	++	+	+	+	+	
Vertebrae	++	++	++	+	+	+	High rates of hematopoietic marrow are maintained throughout life, but there is considerable individual variability in that pattern found within and between vertebra types (Ricci et al., 1990)
Sacrum	++	++	++	++	++	++	Clinical work on the sacrum is more limited than many other skeletal areas

Notes: ++ spaces in bone largely occupied by hematopoietic marrow and there is a strong possibility of bone changes in response to marrow hyperplasia. + presence of hematopoietic marrow in the form of mixed marrow may maintain patterns of reduced bone relative to that anticipated, particularly where marrow hyperplasia is present. +/- there is routine retention of hematopoietic marrow in the form of mixed marrow alongside developing areas of yellow marrow. - under normal circumstances no further changes associated with marrow hyperplasia would be anticipated although such a pattern may already be present. Data primarily based on studies used to construct Fig. 4.

move beyond just examining the correlation of various skeletal features. Being able to identify those who have been free of skeletal changes associated with marrow hyperplasia will be just as important as identifying those who experienced this condition.

Thin cortices or enlarged inter-trabecular spaces are often in passing mentions in individual clinical case reports (e.g., Resnick and Niwayama, 1988:2341). Agarwal et al. (1970) reported on radiological changes in 100 individuals with acquired anemia. Atrophy of the skull's outer table was relatively common in 90%, and similar levels were reported for thinning of the cortical bone in the hands. Clear widening of the diploic space was reported in just two instances. In the absence of metric evaluation, however, only severely affected cases will have been identified. While these reports (and citations therein) serve a valuable function in demonstrating that anticipated changes based on the basic underlying physiological mechanisms do indeed occur, larger sample numbers with data from a more comprehensive set of skeletal locations and ages are required to build a picture of anticipated 'normal' community levels of bone by age and sex. Such data would contribute to developing metric data sets that can be used to assist in identifying individuals who experienced anemia.

The proposal to approach the diagnosis of anemia primarily through metric evaluation rather than lesions would mark a fundamental shift in consideration of the condition. However, if accepted and applied, it would enable paleopathologists to make significant progress in considering anemia in past communities. The acquisition of data that would support metric evaluation of skeletal changes in response to anemia would need to be approached similarly to investigations of age-related bone loss and osteoporosis; the factors contributing to the development of these conditions were recently reviewed in Brickley et al. (2020: Chapter 6). Issues such as childhood and adolescent skeletal development and peak bone mass, nutrition throughout life, physical activity, pregnancy and lactation, aging, menopause, oxidative stress, and osteoimmunology were considered. In particular, consequences of malnutrition other than anemia have the potential to affect the amount of bone present, so the exact causes of the more general radiographic changes reported on by Agarwal and colleagues (1970) and aspects of thinning and atrophy in poorly nourished children (Burko et al., 1961) cannot be precisely deduced, and these issues also apply to the post-cranial skeleton. Anemia was not explicitly highlighted, although the condition is closely linked to various of these issues. Mays (2006) highlighted that links between poor childhood nutrition and appositional bone growth have consistently been noted in clinical studies; he conjectured that larger medullary cavities observed in some archaeological groups might reflect marrow hyperplasia. There is cognizance of the high level of variability between individuals and population groups and these issues have recently been addressed by Cowgill et al. (2023) who note the contribution of poor general health and nutrition on cortical bone area and the need for more data on typical long bone development.

The primary recommendations of this paper, many of which are already standard best practice in paleopathology, are set out below and further details are provided in the discussion that follows:

- Do not infer marrow hyperplasia (evidence for anemia) from either the cranial or post-cranial skeleton where direct evidence of this physiological condition has not been demonstrated, preferably using metric data.
- Take systematic measurements of bones studied from x-ray, CT- or micro-CT images. For both the post-cranial and cranial skeleton measurements that document the relationship between relative amounts of cortical bone and space that will have been occupied by marrow during life are recommended as the starting point.
- Consider using indices or ratios and report full data on the various components that bone and marrow space that make up indices or ratios.
- Data should be reported by age and sex where known or estimated.
- Measurements employed need to be clearly described. Any non-standard measurements need sufficient methodological information that they can be readily repeated by others.
- As a minimum intra-observer error should be reported, and for any measurement that is not firmly established inter-observer error should also be reported (see Mays, 2023).
- Clear information on equipment used and all instrument settings must be provided. Resolution varies considerably, but in order to evaluate marrow hyperplasia as a minimum researchers need to be able to clearly differentiate between cortical and trabecular bone or medullary space.
- Anemia diagnosis based on metrics should be approached using statistical evaluation. In addition to employing indices and ratios techniques such as multivariate statistical analysis can be used to analyze the effect of marrow hyperplasia on bone and allows the effects of confounding variables such as the contribution of normal age and sex related changes in bone dimensions with growth, development and aging to be considered.

Early paleopathological work on anemia did provide some data on cranial metric assessments by age (see Angel, 1966). Nonetheless, even though supplemental data can now readily be added to journal papers, such data have and continues to only appear in non-peer-reviewed theses (see Stuart-Macadam,1982 and Durdin, 2020), which contains data supporting statements on cranial thickness by O'Donnell et al. (2023). Going forward, the inclusion of metric data in supplemental files in the sharing advocated for by Buikstra et al. (2022) is required to advance the iterative process of building metric data sets to evaluate evidence for anemia in both the cranial and post-cranial skeleton and making comparisons.

5.3.1. Developing data sets: evidence of marrow hyperplasia in the post-cranial skeleton

Evaluation and quantification of aspects of cortical bone have a long history in paleopathology, likely because cortical thickness is relatively simple to evaluate (e.g., van Gerven et al., 1969; Mays, 1996; Ives and Brickley, 2005; Gilmour et al., 2021). Datasets allowing comparison to more recent groups are available (e.g., Virtama and Helelä, 1969), and such data are readily gathered and broadly comparable in both modern and archaeological individuals. For example, the large radiogrammetric study using recent individuals from Finland undertaken by Virtama and Helelä (1969); Helelä et al. (1969) was primarily aimed at understanding patterns of bone loss and susceptibility to fracture; this is how this dataset has been used in studies of archaeological bone to date (e.g., Mays, 1996; Beauchesne and Agarwal, 2014) but it contains some individuals still undergoing growth and development. Aspects of the data could be used in multivariate analysis to allow for the contribution of anticipated bone changes according to age and sex to be controlled for. Bone mineral density data could also be used. Such data are gathered from across the skeleton, frequently from regions with a high trabecular bone content such as the vertebrae, hip and wrist (e.g., Melton et al., 2003; Bliuc et al., 2015). As discussed below these are regions in which marrow hyperplasia might effect skeletal structures and so such data could be a valuable component in multivariate evaluations of evidence of marrow hyperplasia.

In data sets such as those provided by Virtama and Helelä (1969), and other reported data for normal growth and development, hematologic data are not considered as part of the exclusion criteria. Given the current clinical incidence of anemia, individuals with cases that escaped clinical attention (Maakaron, 2021) will be included and there may well be individuals who had received a diagnosis at some stage of life. Use of 'unknown' data for normal age-related patterns will simply result in very conservative results being generated. Ideally paleopathologists will start to develop data sets working collaboratively with clinicians, and this will enable more precise indices and ratios to be developed.

The only bones listed in Table 2 that currently have widely accepted

measurements with published data sets are the metacarpals and phalanges of the hand (Virtama and Helelä, 1969). The proximal and distal regions of long bones tend to be the location of structural changes, such as coarsened trabeculae in clinical case reports of those with acquired anemia (e.g., Aksoy et al., 1966). Such changes occur in multiple conditions, and evaluation will be highly subjective. Only the most extreme cases are likely to be noticed with visual assessment, meaning metric evaluation of microarchitectural changes to trabecular bone is preferable. As suggested by Saint-Martin et al. (2015:41), it would be relatively easy to implement metric evaluation of features arising because of marrow hyperplasia, such as dimensions and structural arrangements of trabeculae. Older work, such as Brickley and Howell (1999), used invasive techniques to evaluate trabecular microarchitecture, however, recent developments in Micro-CT technologies could revolutionize this type of research. For example, Kurki et al. (2022) work on the implications of appositional growth for measuring aspects of the cross-sectional geometry of long bones has considerable positive implications for studies considering marrow hyperplasia during growth and development.

5.3.2. Developing data sets: evidence of marrow hyperplasia in the cranial skeleton

Aspects of metric evaluation set out in Features 2–4 of Table 1 have been used in both older clinical (e.g., Reynolds, 1965; Sebes and Diggs, 1979) and paleopathological work (e.g., Angel, 1966; Stuart-Macadam, 1987; Panzer et al., 2023). However, the resolution capacity of CT equipment used recently by Panzer et al. (2023) and the lack of information on porotic lesions likely contributed to these authors giving metric evaluation such a prominent role in their work. Evaluating this work and older work by Stuart-Macadam (1987) forms a basis for the proposal presented here for a framework to evaluate cranial thickness, evidence of diploic expansion, and cortical thinning either with standard radiographic or CT analysis.

Although at present ratios have only been established clinically for the frontal and parietal bones (Reynolds, 1965; Sebes and Diggs, 1979) it is recommended that measurements should be obtained to calculate the ratio of compact to diploic bone are also calculated for the occipital and temporal bones at the locations described in Table 3. The point of greatest calvarial diameter (see Reynolds, 1962) should also be measured for the frontal bone where the target measurement site does not fall on this point or is absent or damaged (at worst such measurements would underestimate evidence of marrow hyperplasia). Researchers need to ensure the correct identification of incomplete bones in individuals still undergoing growth and development. Panzer et al. (2023) provides clear information on metric evaluation of the frontal bone (summarized in Table 3 and Fig. 5).

The measurements suggested by the Panzer *ibid.* are more straightforward to apply than those put forward by Stuart-Macadam (1987); these were never widely employed. The recommended simpler framework with provision for fragmented bones should see wider adoption. Evaluating multiple cranial bones will enable more to be learned about evidence for disease occurrence and potential recurrence across the life course (see Section 5.2 and Fig. 6). Critically for broader applicability, these measurements can be obtained on either standard radiographs or CT-generated images.

Panzer et al. (2023) adopted the ratio of compact to diploic bone of 1:2.5, which they report to be conservative; the potential that it may have underestimated cases of marrow hyperplasia is discussed. Without clinical criteria for diagnosing anemia (Section 3), paleopathologists have been forced to rely on limited publications dealing with genetic anemia (e.g., Sebes and Diggs, 1969), so care is required. However, it would be worth actively integrating biological approaches and

Table 3
Recommended cranial measurements.

Bone	Description of location measurements performed
Frontal	1. On CT scans on a median sagttal MPR above the orbital roof and nasal bone, or equivalent measurement on a sagittal radiograph, see Fig. 6. Measurement should be taken as close to the medial point above the nasal bones as possible above the most superior point of the orbital plate. 2. At the point of greatest width, if this is a different location to Measurement 1. The ratio of compact to diploic bone1:2.5 has been used as the cut-off point for those with marrow hyperplasia having results above this level.
Parietal	1. At the point of greatest width on CT scans on a coronal MPR for each side at the point of greatest width, or equivalent measurement on a coronal radiograph. The ratio of compact to diploic bone1:2.5 has been used as the cut-off point for those with marrow hyperplasia having results above this level.
Occipital	1. At the point of greatest width superior to the nuchal line (avoiding the occipital crests or protuberances) on CT scans on a median sagittal MPR or equivalent measurement on a sagittal radiograph. The cut-off point for ratios of compact to diploic bone for those with marrow hyperplasia has yet to be established for this bone.
Temporal	1 & 2. On a coronal MPR for each side at the point of greatest width within the pars squamosa of the temporal bone. The cut-off point for ratios of compact to diploic bone for those with marrow hyperplasia has yet to be established for this bone.

Notes: All measurements are two-dimensional and should be made perpendicular to the inner table of the cranial vault. Measurements adapted from Panzer et al. (2023):3–4, and Ebel et al. (1995) in German language were consulted for information on Measurement 1 of the frontal bone. MPR = multiplanar computed tomography reconstruction.

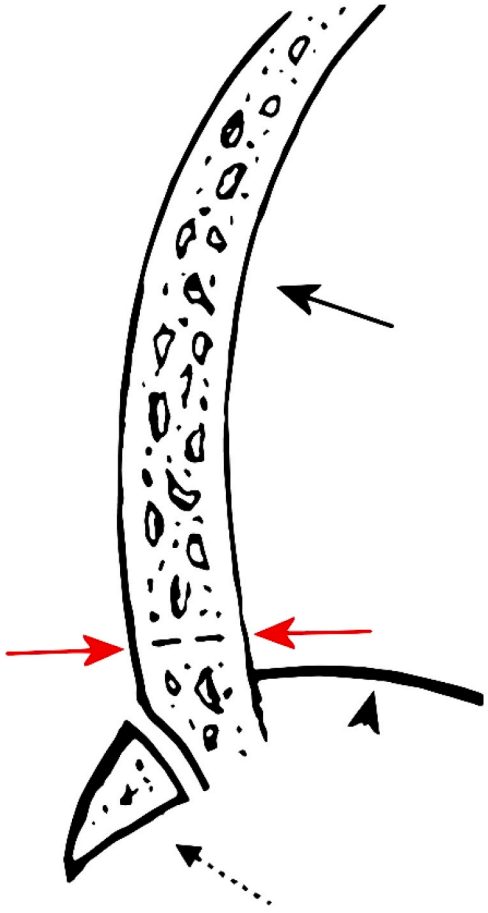

Fig. 5. Measurement of the cranial vault thickness of the frontal bone. (a) Schematic drawing, according to Ebel illustrating the measurement (red arrows) of the frontal bone (black arrow) above the nasal bone (dotted arrow) and orbital roof (arrowhead) on x-rays (Ebel et al., 1995). Reprinted from Panzer et al. (2023). Anemias in ancient Egyptian child mummies: Computed tomography investigations in European museums. *Int. J. Osteoarchaeol.*, Fig. 4,ith permission from John Wiley & Sons.

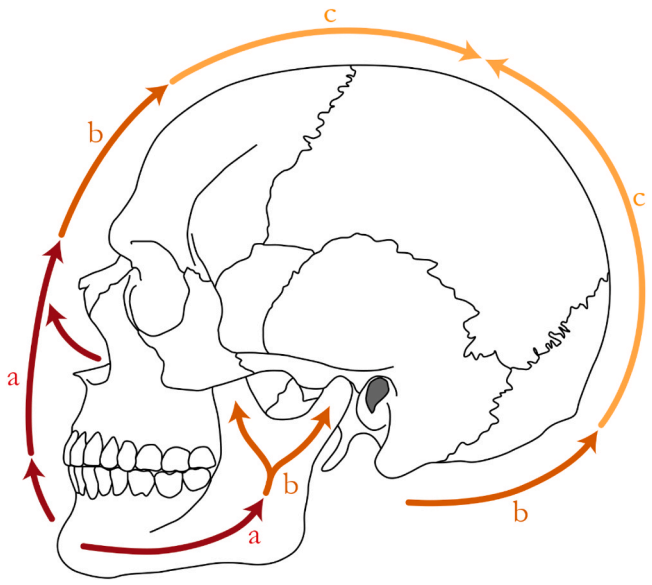

Fig. 6. Pattern of red to yellow bone marrow conversion in the mandible and cranial bones. Conversion occurs in the broad direction indicated by the arrows, starting in the area labelled a, then progressing to areas b and c. Data for the compilation of the figure was drawn from the following sources: Kaneda et al. (1996), Kricun (1985), Ricci et al. (1990), Yamada et al. (1995), Vahlensieck and Layer (2016, Figure 11.6a–d). Conversion from red to mixed marrow has normally occurred by age 11 in the regions labelled "a" and 11–15 years in regions labelled "b". Conversion to predominantly yellow marrow follows these changes. Changes in the area labelled "c" are more variable, but these will be mainly mixed marrow by age 25 and many individuals will have substantial amounts of yellow marrow by age 30. Reproduced from Brickley (2018) Cribra orbitalia and porotic hyperostosis: A biological approach to diagnosis. *American Journal of Physical Anthropology*, *167*, 896-902. Page 899, Fig. 2, with permission from John Wiley & Sons.

considering changes across the skeleton. Obtaining measurements for the suggested ratio will also allow evaluation of outer table thinning. Adopting the publication of complete data sets as recommended would facilitate easy consideration of any aspect of cranial dimensions and re-calculation of ratios.

Micro-CT is growing in use, and a method has recently been proposed to allow the comparison of low- resolution clinical data on trabecular bone morphology with high-resolution CT data from archaeological bone (Saers et al., 2021). The 3D, multi-slice nature of data generated means, depending on the resolution of scans employed, it has considerable potential for evaluation of bone structural parameters and any associated bone foramina (perforations of the bone). As shown in various studies, comparability of CT evaluation and direct examination of bone with results obtained is dependent on the resolution of scans (e.g., Anderson et al., 2021). Nonetheless, considerably more data are now available non-destructively than were obtained using sections of bone (e.g., Brickley and Howell, 1999; Wapler et al., 2004).

6. Conclusions

The lack of consensus on how best to approach the investigation of anemia in paleopathology likely arises from confounding factors in the ubiquity of porotic lesions and limited age-related occurrence of porotic lesions in cases of anemia. Paleopathologists need to stop placing porotic lesions at the center of efforts to diagnose anemia. Recognition of the limitations of porotic lesions to diagnose anemia and the development of diagnostic parameters based on direct measures of evidence of marrow hyperplasia would enable greater confidence in approaching the diagnosis of acquired anemia in past communities. Explicit consideration of microarchitectural changes in bone in response to marrow hyperplasia, alongside metric assessment, coupled with more thoughtful use of porotic and other skeletal lesions, would facilitate far more effective consideration of anemia in past groups. The proportion of those who died at different stages of life with structural changes in bones across the skeleton indicative of marrow hyperplasia needs to be evaluated alongside the presence and absence of lesions. All these factors are required to properly consider the life course approach and aspects of frailty raised in the osteological paradox (Wood et al., 1992).

Much of the disagreement and failure to reach a consensus is because only part of the picture is being considered. Differences between clinical and biomedical work and that undertaken by paleopathologists have yet to be fully considered, and diagnoses made by paleopathologists often step beyond the available evidence. At the same time, there is still a tendency to undervalue paleopathology data and assume that clinical work will somehow produce the 'truth'. Each is different, and fully embracing differences and developments in both disciplines alongside collaborative interdisciplinary partnerships will result in a more productive approach to paleopathological studies of anemia and porotic lesions in past communities.

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Declaration of Competing Interest

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