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Perspectives

The Causes of Porotic Hyperostosis and Cribra Orbitalia: A Reappraisal of the Iron-Deficiency-Anemia Hypothesis

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ABSTRACT Porosities in the outer table of the cranial vault (porotic hyperostosis) and orbital roof (cribra orbitalia) are among the most frequent pathological lesions seen in ancient human skeletal collections. Since the 1950s, chronic iron-deficiency anemia has been widely accepted as the probable cause of both conditions. Based on this proposed etiology, bioarchaeologists use the prevalence of these conditions to infer living conditions conducive to dietary iron deficiency, iron malabsorption, and iron loss from both diarrheal disease and intestinal parasites in earlier human populations. This iron-deficiency-anemia hypothesis is inconsistent with recent hematological research that shows iron deficiency per se cannot sustain the massive red blood cell production that causes the marrow expansion responsible for these lesions. Several lines of evidence suggest that the accelerated loss and compensatory overproduction of red blood cells seen in hemolytic and megaloblastic anemias is the most likely proximate cause of porotic hyperostosis. Although cranial vault and orbital roof porosities are sometimes conflated under the term porotic hyperostosis, paleopathological and clinical evidence suggests they often have different etiologies. Reconsidering the etiology of these skeletal conditions has important implications for current interpretations of malnutrition and infectious disease in earlier human populations. Am J Phys Anthropol 139:109–125, 2009.

Porotic hyperostosis, identified macroscopically as circumscribed areas of pitting and porosity on the external surface of the cranial vault, and cribra orbitalia, a similar condition seen in the orbital roofs, are two of the most commonly reported pathological conditions in archaeological collections of human skeletal remains (Figs. 1 and 2). Although these lesions are often produced by the expansion of the diploë (spongy bone) of the skull in response to marrow hypertrophy, other pathological processes such as those associated with chronic scalp infections and scurvy can also produce porosities in the external surface of the cranial vault (Ortner, 2003). Angel first introduced the term "porotic hyperostosis" in 1966 as a descriptively more appropriate alternative to the term "symmetrical osteoporosis" that earlier authors had used for the same condition (Hrdlicka, 1914; Williams, 1929; Jarcho et al., 1965; Moseley, 1965; Angel, 1966, 1967). He noted similarities in the probable etiologies of the cranial vault and orbital roof lesions and suggested porotic hyperostosis as an overarching term that could encompass both conditions. Bioarchaeologists have documented both conditions in prehistoric and historic contexts worldwide and commonly use them in assessing the health and nutritional status of earlier human populations (i.e. El-Najjar, 1967; Zaino and Zaino, 1975; El-Najjar and Robertson, 1976; El-Najjar et al., 1976; Cohen and Armelagos, 1984; Walker, 1985; Walker, 1986; Mensforth, 1991; Mittler and Gerven, 1994; Pechenkina et al., 2002; Steckel and Rose, 2002).

Since the 1950s, iron-deficiency anemia has gained acceptance as the most likely cause of the marrow hypertrophy that produces porotic hyperostosis. This inference is based principally on analogies with modern clinical cases in which hematological evidence of iron-deficiency anemia and radiographic evidence of cranial vault marrow hypertrophy co-occur (Sheldon, 1936; Eng, 1958; Britton et al., 1960; Shahidi and Diamond, 1960; Burko et al., 1961; Jelliffe and Blackman, 1962; Powell et al., 1965; Aksoy et al., 1966; Lanzkowsky, 1968; Agarwal et al., 1970; Moseley, 1974).

Epidemiological data have also been used to support the theory that porotic hyperostosis and cribra orbitalia are osseous responses to iron-deficiency anemia. From radiographic and gross anatomical studies, it is clear that the severe forms of hereditary hemolytic anemia such as

We dedicate this to the memory of Phillip Walker; by his example, we are inspired.

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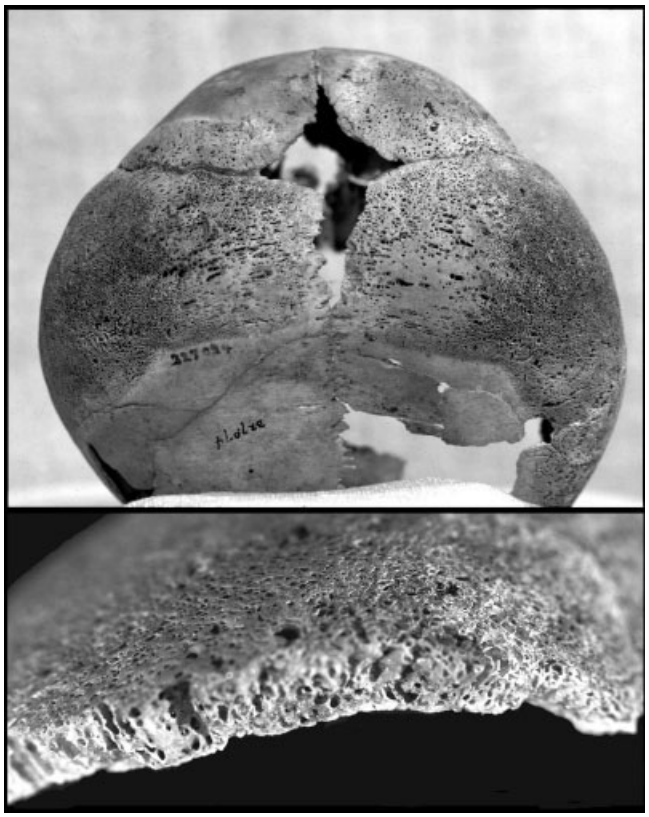

Fig. 1. Porotic hyperostosis. Top: A superior-posterior view of porotic hyperostosis in a 3 year old Native American child from Pueblo Bonito, New Mexico dating from between AD 950–1250 (U.S. National Museum of Natural History specimen 327074). Bottom: Close-up view of a section through the skull of the same individual showing expansion of the diploë and loss of the outer table owing to marrow hypertrophy (Photographs courtesy of Donald Ortner).

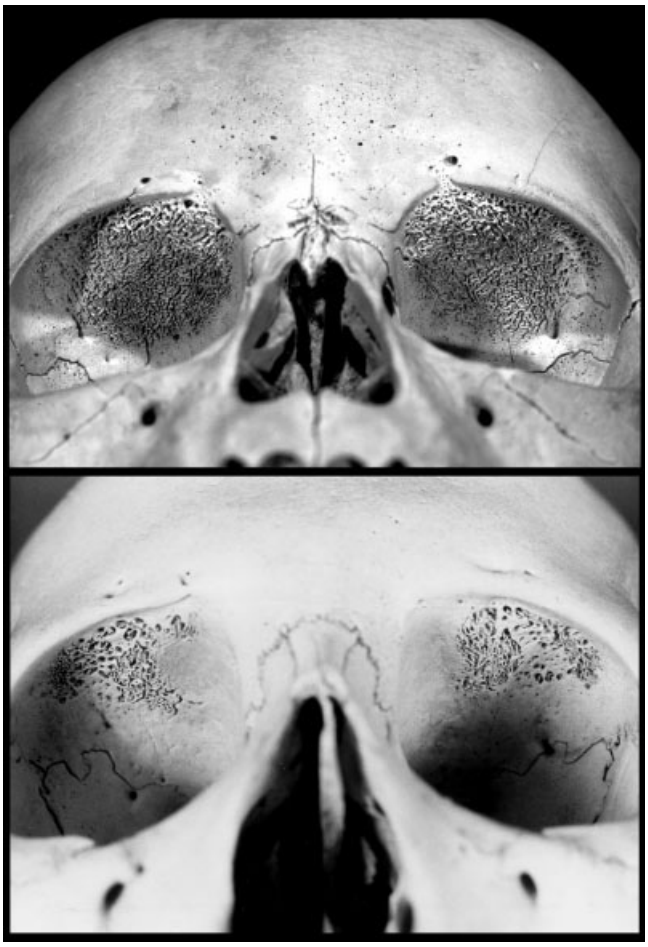

Fig. 2. Cribra orbitalia. Top: "active" orbital lesions in the skull of a 4-year-old XII Dynasty child from Lisht Egypt. The new bone formation is probably in part a response to subperiosteal bleeding associated with scurvy (U.S. National Museum of Natural History specimen 256571, photo courtesy of Donald Ortner). Bottom: "healed" cribra orbitalia lesions in an unprovenienced anatomical specimen.

thalassemia major and sicklemia produce porotic hyperostosis (Caffey, 1937; Sebes and Diggs, 1979; Hershkovitz et al., 1997). However, these hereditary conditions are either so rare or population specific that they can hardly account for the widespread occurrence of porotic hyperostosis and cribra orbitalia in archaeological collections (Walker, 1985; Palkovich, 1987; Sullivan, 2005). Iron-deficiency anemia, in contrast, is a worldwide health problem associated with poor living that currently afflicts between 500 million and 600 million people in developing countries (Bothwell, 1995). The prevalence of porotic hyperostosis and cribra orbitalia in archaeological collections thus exhibits clear epidemiological parallels with iron deficiency anemia: both are common conditions found in archaeological contexts suggesting poor sanitation, diets deficient in essential nutrients, and infectious disease (Hengen, 1971; Walker, 1985; Walker, 1986; Schutkowski and Grupe, 1997; Blom et al., 2005).

These correlations have convinced many paleopathologists that porotic hyperostosis and cribra orbitalia are osseous responses to iron-deficiency anemia. This etiological evidence is so widely accepted that porotic hyperostosis and cribra orbitalia have almost become synonymous with iron-deficiency anemia in the bioarchaeological literature (Stodder, 2006).

In this article, we show that anemias causing premature red blood cell (RBC) death and increased erythropoiesis (RBC production), such as the megaloblastic and hemolytic anemias, provide a much more likely explanation for porotic hyperostosis than does iron-deficiency anemia. Although cribra orbitalia may also frequently be caused by megaloblastic and hemolytic anemia, paleopathological studies suggest that these lesions have a more complicated etiology that sometimes includes the subperiosteal bleeding associated with nutritional deficiencies such as scurvy. Reconsidering the etiology of these skeletal conditions has important implications for current interpretations of malnutrition and infectious disease in earlier human populations.

ANEMIA AND POROTIC HYPEROSTOSIS

Anemia is a pathological symptom, not a specific disease. Literally meaning "without blood," anemia is defined as a pathological deficiency in either RBCs or the hemoglobin they contain. In a healthy homeostatic state, bone marrow RBC production equals the rate at which these cells are destroyed. There are three principal causes of anemia: blood loss, impaired erythropoiesis, and increased hemolysis (RBC destruction). These

TABLE 1. Age distribution of individuals with cribra orbitalia and porotic hyperostosis in the History of Health in the Western Hemisphere database (Steckel et al., 2002) who could be scored for both conditions

Age group	Cribra orbitalia			Porotic hyperostosis			Total
	Absent	Present	% with	Absent	Present	% with	
0–<5	514	220	30.0	612	122	16.6	734
5–<10	160	116	42.0	227	49	17.8	276
10–<15	132	53	28.6	142	43	23.2	185
15–<20	236	55	18.9	244	47	16.2	291
20–<25	278	57	17.0	283	52	15.5	335
25–<30	320	57	15.1	315	62	16.4	377
30–<35	367	49	11.8	366	50	12.0	416
35–<40	641	85	11.7	618	108	14.9	726
40–<45	326	51	13.5	333	44	11.7	377
45–<50	271	68	20.1	303	36	10.6	339
50–<55	125	25	16.7	133	17	11.3	150
55–<60	111	15	11.9	114	12	9.5	126
60–<65	37	3	7.5	39	1	2.5	40
65+	42	5	10.6	43	4	8.5	47
Total	3,560	859	19.4	3,772	647	14.6	4,419

anemia-producing conditions are not mutually exclusive and often co-occur in the same individual.

From an etiological perspective, the anemias fall into two categories: genetic and acquired. Genetic anemias (e.g., thalassemia and sicklemia) are rare in comparison to the acquired anemias caused by blood loss and nutrient deficiencies. The nutrients required for maintaining RBC homeostasis include essential amino acids, iron, and vitamins such as A, B_{12}, B_6, and folic acid (Martini and Ober, 2001). Iron is a key constituent of hemoglobin and thus iron deficiency is the most common cause of anemia (Ponka, 1997). Although blood loss is a frequent cause of iron-deficiency, it also can result from iron deficient diets, gastrointestinal iron malabsorption, or various combinations of these factors. When the intake or absorption of iron or other essential nutrients is insufficient, RBC production is hampered and anemia ensues.

The body mounts a hierarchical response to anemia, resorting to cranial vault marrow expansion and remodeling only after less costly measures fail to maintain homeostasis. RBCs normally mature over a seven-day period and have a lifespan of about 120 days. When anemic conditions cause hemoglobin levels to drop, the body becomes oxygen starved. This hypoxic state triggers the release of erythropoietin, a hormone produced by the kidneys, that accelerates RBC production and maturation (Halvorsen and Bechensteen, 2002; Fandrey, 2004; Stockmann and Fandrey, 2006).

If this hormonal response proves inadequate, the skeletal centers of hemopoietic marrow are stimulated to increase RBC production (Ross and Logan, 1969). In the cranial vault, expansion of the diploë occurs at the expense of the outer table, which is gradually resorbed. This resorption creates the porosities that give porotic hyperostosis lesions their characteristic "spongy" appearance (see Fig. 1). In extreme cases of anemia, such as those seen in cases of thalassemia major, the diploë hypertrophies far beyond the original ectocranial surface to create palpable bosses and a distinctive "hair-on-end" effect that is readily observed in radiographs (Hooton, 1930; Caffey, 1951; Eng, 1958; Lanzkowsky, 1968; Stuart-Macadam, 1987).

Based on these anatomical studies, it is clear that porotic hyperostosis is a sign of anemia; these cranial vault porosities are produced by the marrow expansion within the diploë of the skull that occurs as part of a systemic response to RBC and hemoglobin insufficiencies (Moseley and Jarcho, 1966; Moseley, 1974; Schultz, 2001; Ortner, 2003). Of the many forms of anemia, not all of them produce the massive marrow hypertrophy that is responsible for porotic hyperostosis. Marrow hypertrophy is a result of elevated mature RBC production; only those anemias with the potential to stimulate and sustain high levels of erythropoiesis can logically be linked to the bone marrow hyperplasia responsible for porotic hyperostosis.

POROTIC HYPEROSTOSIS IN CHILDHOOD

The distribution of RBC-production sites within the body changes during development (Hoffbrand and Lewis, 1981; Halvorsen and Bechensteen, 2002). In utero, fetal erythropoiesis occurs first in the yolk sac, followed by RBC production in the spleen and liver, and then in the bone marrow. During childhood and adolescence, the diploë of the cranial vault bones and medullary cavities of the long bones are the main RBC production sites. In adults, most erythropoiesis occurs in the spongy bone of the vertebral, sternal, and costal regions of the axial skeleton (Hoffbrand and Lewis, 1981).

Based on this shift in the loci for RBC production, it has been convincingly argued that porotic hyperostosis and cribra orbitalia most likely reflect childhood anemia (Stuart-Macadam, 1985; Kent, 1986; Stuart-Macadam, 1992). This conclusion is supported by the fact that active porotic lesions (those showing little evidence of remodeling) are almost entirely confined to the skeletons of children and adolescents in archaeological collections (see Fig. 1). Healed lesions, in contrast, are typical of older adults (Stuart-Macadam, 1985; Walker, 1985, 1986).

These bioarchaeological data accord well with modern clinical evidence showing that children have a reduced capacity to sustain elevated RBC production (Halvorsen and Bechensteen, 2002). These age-related changes in marrow production coupled with the association between severe anemia and elevated rates of child mortality (Scrimshaw, 1991) are consistent with bioarchaeological studies that show porotic hyperostosis is much more common in the skeletons of children than it is in those of adults (Table 1, Fig. 3).

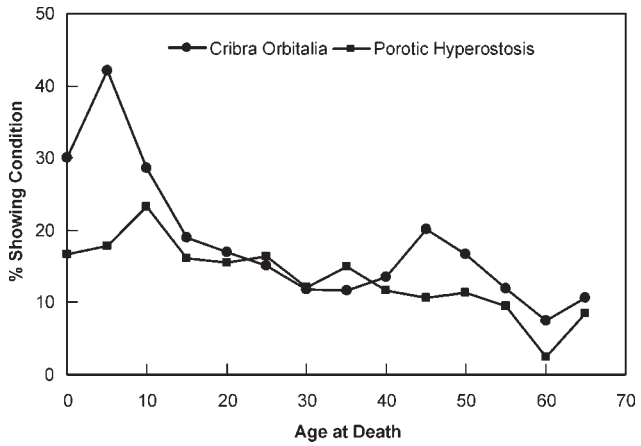

Fig. 3. Age distribution of individuals with cribra orbitalia and porotic hyperostosis in the History of Health in the Western Hemisphere database (Steckel et al., 2002) who were scored for both conditions.

IRON-DEFICIENCY INHIBITS MARROW HYPERTROPHY

Iron is a key component of hemoglobin and sufficient iron stores are thus necessary for RBC production (Ponka, 1997:1). Iron-deficiency anemia is a pervasive global health problem that has stimulated an enormous amount of recent epidemiological and pathophysiological work. This research has important paleopathological implications; it is now generally accepted that iron deficiency impedes both hemoglobin synthesis and the formation of mature erythrocytes with adequate hemoglobin content. Iron-deficiency-induced anemia thus results, at least in part, from reduced RBC production (Brugnara, 2003; Arndt et al., 2005; Thomas and Thomas, 2005; Kempe et al., 2006). This reduced erythropoiesis is linked to levels of the protein-synthesis inhibitor, heme-regulated eIF2α kinase (Han et al., 2001; Ron, 2002; Brugnara, 2003; Furuyama et al., 2007) that serves to regulate the production of RBCs while protecting mature RBCs from premature destruction. The simple fact that iron-deficiency anemia effectively decreases mature RBC production means that it cannot possibly be responsible for the osseous expression of hemopoietic marrow expansion that paleopathologists recognize as porotic hyperostosis and cribra orbitalia.

Hemolysis plays a central role in the complicated feedback system responsible for stimulating RBC production. In its absence, the marrow hypertrophy that causes porotic hyperostosis cannot occur. Although there is some evidence that iron-deficient erythrocytes have a decreased lifespan (Ramachandran and Iyer, 1984; Kempe et al., 2006), this effect is modest in comparison to the massive erythrocyte mortality associated with the hereditary hemolytic anemias that are known to produce porotic hyperostosis (Kaplan and Zuelzer, 1950; Temperley and Sharp, 1962).

In any event, because iron is necessary to sustain erythropoiesis, iron-deficiency anemia cannot logically be linked to cranial lesions produced by marrow hypertrophy. Iron-deficiency anemia reflects a state of inadequate blood production; it does not involve massive RBC destruction. When iron stores are adequate to sustain erythropoiesis, the body compensates for RBC loss or destruction by expanding the volume of the RBC-producing hemopoietic bone marrow (Metcalf, 1969; Berliner and Duffy, 1995). Sufficient iron stores, which are not present in a clinical state of severe iron-deficiency, are necessary for this response to occur. Thus, anemias resulting from hemolysis and functioning but ineffective erythropoiesis, such as megaloblastic and hemolytic anemias, provide a much more plausible etiological explanation for porotic hyperostosis than does iron-deficiency anemia.

CAUSES OF MARROW HYPERTROPHY

In sharp contrast to iron-deficiency anemia, the megaloblastic and hemolytic anemias do have the capacity to trigger the massive marrow hypertrophy that produces porotic hyperostosis. Hemolytic anemia results from premature RBC destruction (hemolysis) that overwhelms the capacity of hemopoietic bone marrow to compensate for these losses through RBC production (Antony, 1995). When RBC destruction exceeds the rate of RBC production, this stimulates compensatory bone marrow expansion. There are over 200 types of hemolytic anemia. These conditions result from either intrinsic (within the RBC) or extrinsic (outside the RBC) factors. The hereditary forms of hemolytic anemia, such as thalassemia and sicklemia, are the result of molecular defects within the RBC. Extrinsic factors causing marrow hypertrophy include toxins, drug use, cyanotic heart disease and certain forms of cancer (Schrier, 1995).

Megaloblastic anemias can trigger the same hemolytic marrow-expansion mechanism as hemolytic anemia. Chronic dietary deficiencies and malabsorption of vitamin B_{12} and/or folic acid are the most common causes of megaloblastic anemia. It is characterized by enlarged hemopoietic cells (macrocytes) with large nuclei resulting from defective DNA synthesis (Koury et al., 2000). The affected marrow cells are unable to divide normally and this results in inefficient erythropoiesis. A feedback cycle ensues that perpetuates marrow expansion as the body continually attempts to compensate for premature deaths of defective RBCs.

Both hemolytic and megaloblastic anemias involve marrow-hypertrophy-inducing overproduction of RBCs. Thus, these are the kinds of anemia that are most likely responsible for the osteological evidence of anemia we see in the bioarchaeological record.

THE IRON-DEFICIENCY-ANEMIA HYPOTHESIS

The link between porotic hyperostosis and anemia was initially established through the identification of identical skeletal changes in patients suffering from severe hemolytic anemias such as thalassemia major and sicklemia. Angel (1964, 1966, 1967, 1984) noted the presence of porotic hyperostosis in ancient skeletal remains in the Anatolian region where thalassemia and sicklemia are endemic, and suggested these hereditary hemolytic anemias were a possible cause. Skeletal lesions in ancient South Asian archaeological collections led Kennedy (1984) to similar conclusions. Although porotic hyperostosis is not present in skeletons from a 4,000-year-old coastal site in Thailand, thickened facial bones and postcranial porosities suggest the possible presence of thalassemia among these early southeast Asians (Tayles, 1996). As Thayles notes, this absence of an important diagnostic criterion may be explained by clinical studies that show porotic hyperostosis is present only in a small proportion (5–20%)

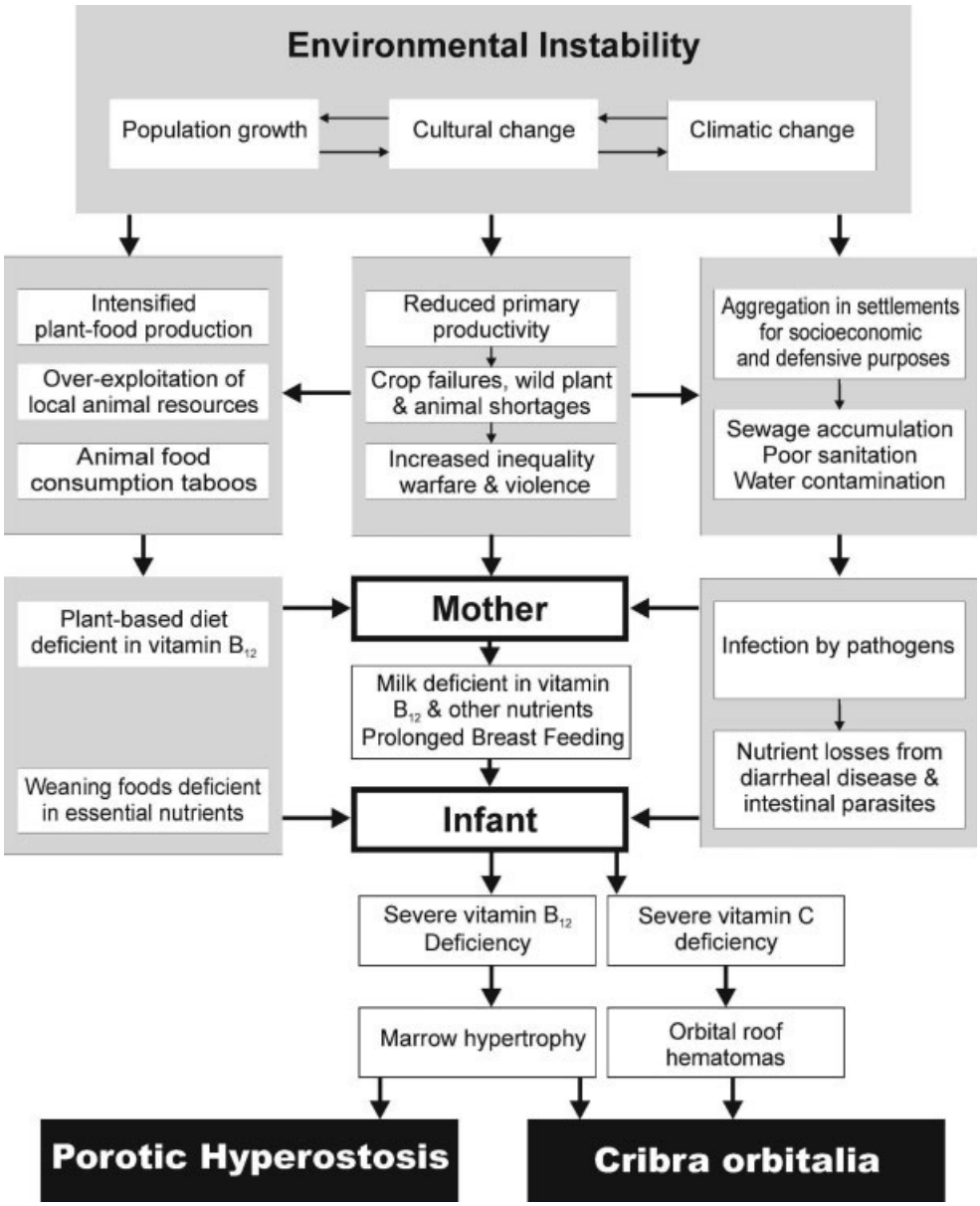

Fig. 4. Flow chart illustrating the relationships of variables related to the etiology of porotic hyperostosis and cribra orbitalia.

of thalassemia cases (Fernbach, 1984; Silverman et al., 1985; Tayles, 1996).

Angel's hypothesis that a hereditary hemolytic anemia, such as thalassemia, was one of the causes of porotic hyperostosis seemed reasonable for Old World skeletal collections from malarial areas. This postulated association between porotic hyperostosis and the hereditary hemolytic anemias, however, was problematic for paleopathologists working with ancient New World collections; malaria, the selective pressure maintaining the alleles responsible for thalassemia and sicklemia in circum-Mediterranean populations, was almost certainly absent from the Western Hemisphere during pre-Columbian times (Dunn, 1965; McNeill, 1976; de Zulueta, 1994).

The ancestral remains of modern Native Americans, such as the members of the Hopi and Zuni in the southwestern United States, display some of the highest known frequencies of porotic hyperostosis (El-Najjar et al., 1975; Walker, 1985). Since these modern Native Americans do not have high rates of hereditary hemolytic anemia, iron-deficiency anemia was focused on as the most likely alternative explanation. Although the simplicity of this iron-deficiency-anemia hypothesis is appealing, as discussed above, our current knowledge of the relationship between iron availability and marrow hypertrophy is sufficient to rule out iron-deficiency per se as the cause of porotic hyperostosis.

THE CAUSES OF POROTIC HYPEROSTOSIS

Without an endemic, hereditary, hemolytic anemia that can explain the widespread occurrence of porotic hyperostosis in ancient New World populations, what are the most likely alternative explanations? Although iron-

deficiency anemia can also be ruled out on hematological grounds, the extensive work by researchers attempting to establish a causal relationship between iron-deficiency anemia and porotic hyperostosis does clearly implicate dietary deficiencies and unsanitary living conditions in its etiology. We argue that the synergistic effects of nutritionally inadequate diets, poor sanitation, infectious disease, and cultural practices related to pregnancy and breastfeeding provide a plausible explanation for the high rates of porotic hyperostosis found in many prehistoric populations (see Fig. 4).

Megaloblastic anemia of nutritional origin

Marrow hypertrophy in response to a nutritional megaloblastic anemia is the most likely explanation for the common occurrence of porotic hyperostosis in New World populations. Vitamins B_{12} (cobalamin) and B_9 (folic acid) deficiencies are the most common causes of megaloblastic anemia. Because foods of animal origin are practically the only source of vitamin B_{12}, it is a frequent nutritional deficiency of strict vegetarians, and commonly coexists with deficiencies of iron and other nutrients derived primarily from animal foods (Stabler and Allen, 2004). Patients with vitamin B_{12} deficiency that develop megaloblastic anemia exhibit symptoms of nervous system demyelination including irritability, abnormal reflexes, various psychiatric disorders, and reduced alertness progressing to coma (Hector and Burton, 1988; Graham et al., 1992; Shanoudy and Salem, 1992; Lerner and Kanevsky, 2002). There is also evidence that fetuses exposed to B_{12} deficiency in utero have postnatal immune function problems that increase their susceptibility to infections (Newberne and Young, 1973).

Because adults normally have substantial vitamin B_{12} stores in their livers, they develop vitamin B_{12} deficiency very slowly and may remain asymptomatic despite consuming a vitamin B_{12} deficient diet for many years (Goodman and Salt, 1990). Infants, in contrast, have very meager vitamin B_{12} reserves and can develop symptoms of deficiency within months of their birth, especially when breastfed by mothers whose own vitamin B_{12} reserves are depleted (Turner et al., 1999; Casella et al., 2005; Cetinkaya et al., 2007).

The nutritional problems of modern vegans with strict beliefs about avoiding animal products provide a model for the nutritional predicament faced by mothers in ancient societies who were forced to adopt similar diets because of food-production-system failures, overexploitation of local animal resources, famines, and so on. Modern people with diets containing animal products ingest between 3 and 32 μg per day of vitamin B_{12} compared with between 0.00 and 0.25 μg per day for strict vegetarians (Allen, 1994). This is well below the estimated minimum adult daily requirement of 0.50 μg (Baker and Mathan, 1981). Because of their vitamin B_{12} deficient diets, people who rigorously practice vegetarianism or veganism have high rates of megaloblastic anemia (Sanders et al., 1978; Dwyer et al., 1982; Sklar, 1986; Goodman and Salt, 1990; Ambroszkiewicz et al., 2006). For example, 25 infants examined by Shinwell and Gorodischer (1982) who lived in a vegan religious community showed evidence of protein-calorie malnutrition, iron- and vitamin B_{12}-deficiency anemia, rickets, zinc deficiency, and multiple recurrent infections. Likewise, a well-studied group of Dutch children raised in families with a macrobiotic diet exhibited chronic B_{12} deficiency, rickets and growth retardation (Dagnelie et al., 1989; Dagnelie et al., 1990; Dagnelie et al., 1994).

In populations with restricted animal food access, the risks of vitamin-B_{12}-deficiency-induced megaloblastic anemia are greatly increased for nursing infants (Baker et al., 1962; Higginbottom et al., 1978; Sandberg et al., 1981). Pregnant women who have been strict vegetarians, and even those with low animal product consumption, are likely to become vitamin B_{12} deficient during pregnancy and lactation, have low vitamin B_{12} levels in their breast milk, and give birth to vitamin-B_{12}-deficient babies (Cheron et al., 1989; Specker et al., 1990; Allen, 1994; Specker, 1994; Casterline et al., 1997). The low concentration of vitamin B_{12} in the breast milk of vitamin-B_{12}-deficient mothers is transmitted to their infants (Srikantia and Reddy, 1967; Lonnerdal, 1986; Doyle et al., 1989). Although breastfeeding mothers with low vitamin B_{12} levels often do not show signs of anemia, their breastfed babies are likely to develop clinical signs of severe megaloblastic anemia.

Nutritional deficiencies in traditional societies

In many ethnographically documented societies, cultural practices, such as food taboos, limit the access women have to vitamin B_{12}-rich foods of animal origin (Aberle, 1932; Jelliffe and Jelliffe, 1964; Sundararaj and Pereira, 1975; Katona-Apte, 1977; Ebomoyi, 1988; Spielmann, 1989; Harrison, 1992; Marchant et al., 2002). Under such circumstances, customs that encourage prolonged, exclusive breastfeeding can greatly increase the risk of vitamin B_{12} deficiency for babies (Weiss et al., 2004).

This problem of vitamin B_{12}-deficiency-induced megaloblastic anemia would be especially severe in famine situations where breastfeeding is sometimes prolonged because weaning foods other than breast milk are unavailable (Lindstrom and Berhanu, 2000). As a last resort, mothers sometimes also revert to breastfeeding weaned infants in such dire circumstance (Almedon and de Waal, 1990). In other cases, when breast milk fails, the only alternative may be premature weaning on nutrient-poor famine foods.

Such nutritional problems would be all the more likely in hunter-gatherer societies in which prolonged breastfeeding is sometimes practiced (Takeuchi, 1992; Katzenberg et al., 1993; Sellen, 2002; Clayton et al., 2006) and it is customary to restrict the consumption of fresh meat and other nutrient-rich animal foods by menstruating, pregnant, lactating, and nulliparous women (Aberle, 1932; Ebomoyi, 1988; O'Dempsey, 1988; Spielmann, 1989).

Gastrointestinal infections and nutrient loss

In many earlier societies, the likelihood of vitamin B_{12}-deficiency-induced megaloblastic anemia would be further increased by gastrointestinal parasite infections. For example, patients with symptomatic infection by *Giardia lamblia* and *Enterobius vermicularis* (pin worms) have lower vitamin B_{12} levels than asymptomatic patients (Wright et al., 1977; Solomons, 1982; Cordingley and Crawford, 1986; Hjelt et al., 1992; Casterline et al., 1997; Olivares et al., 2002). Infestations with *Ascaris lumbricoides* (giant intestinal roundworm) interfere with both vitamin B_{12} and vitamin A absorption (Brasitus,

1983). Other intestinal parasites (e.g. *Diphyllobothrium latum, Taenia sp.*) cause megaloblastic anemia by depleting the body of vitamin B_{12} (Nyberg, 1963; Cordingley and Crawford, 1986; Vuylsteke et al., 2004).

In people with normal vitamin B_{12} intake, such intestinal parasite-associated losses may not be large enough to stimulate the large-scale marrow hypertrophy that causes porotic hyperostosis. However, if malabsorption and chronic diarrhea are combined with low dietary intake of vitamin B_{12}, severe megaloblastic anemia would likely ensue (Pærregaard et al., 1990). During times of famine, this was probably a common predicament for children in earlier societies with marginal subsistence bases.

Diarrheal disease caused by crowded, unsanitary living conditions can further increase the risks of vitamin-B_{12}-deficiency-induced megaloblastic anemia. Diarrheal disease is currently a leading cause of death among children less than 5 years of age (Fischer Walker and Black, 2007) and undoubtedly was also a major cause of child mortality in earlier human societies. An important synergy exists between malnutrition and diarrheal disease (Keusch and Farthing, 1986); diarrheal disease contributes to the depletion of B-complex vitamins, vitamin C, vitamin E, selenium, and iron (Long et al., 2007), and there is also a 20–60% decrease in caloric intake during diarrhea bouts (Mata, 1992; DuPont, 1993).

Diarrheal disease typically reaches its peak at the time of weaning. This "weanling diarrhea" syndrome is caused by the nutritionally inadequate, bacteriologically unsafe environments children are often exposed to during weaning (Gordon et al., 1963). In many societies, weaning is a protracted process in which babies are administered foods of low nutritional value under unsanitary conditions (Motarjemi et al., 1993). Acute episodes of gastroenteritis acquired under such conditions can produce small intestinal mucosal damage that significantly reduces vitamin B_{12} absorption (Pærregaard et al., 1990). When malabsorption and chronic diarrhea are combined with low vitamin B_{12} intake, as would be the case in many earlier human populations, severe depletion of vitamin B_{12} stores and the development of megaloblastic anemia would be likely. This in turn would result in the marrow hypertrophy that causes porotic hyperostosis.

THE CAUSES OF CRIBRA ORBITALIA

In paleopathological studies, cribra orbitalia has generally been considered a result of the same pathophysiological process that produces porotic hyperostosis (Hengen, 1971; Cybulski, 1977; Stuart-Macadam, 1989). This conclusion is supported by radiographic and histological studies showing that porosities in the orbital roof are often associated with hypertrophy of the underlying marrow space (Koganei, 1912; Williams, 1929; Stuart-Macadam, 1989; Schultz, 2001). Cribra orbitalia and porotic hyperostosis are sometimes both present in the same individual; this further bolsters the theory that they are responses to the same systemic problem.

Correlations with porotic hyperostosis

The association between cribra orbitalia and porotic hyperostosis is not very strong; in some skeletal collections cribra orbitalia is common and porotic hyperostosis rare, in others porotic hyperostosis predominates (e.g.: Walker, 1985, 1986). Cribra orbitalia is a more frequent paleopathological finding than porotic hyperostosis. For example, in the History of Health in the Western Hemisphere data base (Steckel et al., 2002), which includes data on 217 skeletal collections from sites in North and South America, 14.6% of the 4,419 individuals who could be scored for both conditions had porotic hyperostosis and 19.4% had cribra orbitalia (Table 1). Of the 1,506 individuals who had one or both of the conditions, only 26.9% ($n = 405$) had both.

If cribra orbitalia is an earlier, less severe manifestation of the pathological process producing porotic hyperostosis, this might explain the greater prevalence of cribra orbitalia. However, this reasoning is undermined by the fact that porotic hyperostosis frequently occurs in crania lacking cribra orbitalia. Another possibility is that the two lesion types reflect age-related changes in the locus of the body's hemopoietic response to anemia. Finally, it is possible that higher rates of remodeling in the outer table of the cranial vault relative to the orbital roof reduce the ability of paleopathologists to identify porotic hyperostosis lesions in older individuals.

The clinical evidence linking cribra orbitalia to anemia is weak. Medical discussions of this condition are essentially confined to the paleopathological literature. Even in cases of severe hemolytic anemia, only a mild expansion of the small amount of hemopoietic marrow in the orbital roof is noted, if it is present at all (Caffey, 1937; Caffey, 1951; Sebes and Diggs, 1979; Stuart-Macadam, 1987; Hershkovitz et al., 1997). No clinical data exist on possible associations between the modest orbital roof thickening that does occur under such circumstances and porosities like those paleopathologists would identify as cribra orbitalia.

Histological evidence

Further complicating the task of determining the etiology of cribra orbitalia is the fact that marrow hypertrophy is only one of the pathological processes producing porous, cribriform areas in the orbital roof. Histological studies show that, in some populations, cribra orbitalia lesions are often not associated with clear signs of diploëic hypertrophy, but instead with subperiosteal inflammation. In their histological study of cribra orbitalia in a bioarchaeological Nubian population ($n = 85$), Wapler et al. (2004) found that while 43.5% of lesions could be considered anemia-related due to evidence of marrow hypertrophy, 25.8% were the result of subperiosteal inflammation. The cause of an additional 10.6% of the cases could not be determined, and 20.0% were pseudopathologies produced by postmortem erosion of the orbital roof. In this example, most (56.5%) of the individuals exhibiting gross evidence of cribra orbitalia had conditions that could not be specifically attributed to diploëic hypertrophy.

Orbital porosity and subperiosteal hematomas

Although anemia-induced marrow hypertrophy is probably a common cause of cribra orbitalia, other pathological processes such as those associated with scurvy, rickets, hemangiomas and traumatic injuries can produce subperiosteal hematomas that can lead to orbital roof lesions (Wolter, 1979; Griffeth et al., 1997). During the healing process, these blood clots are transformed into plaques of highly vascular, subperiosteal new bone that on gross examination can appear identical to cribra orbitalia (Woo and Kim, 1997; Sabet et al., 2001; Schultz,

2001; Ma'luf et al., 2002; Brickley and Ives, 2006) (see Fig. 2).

Clinical studies show that these orbital roof hematomas most commonly occur in children. This is because the periosteum of children is less firmly attached to the orbital roof than it is in adults (Ma'luf et al., 2002). The density of the blood vessels connecting the periosteum to the underlying bone decreases with increasing age. Both of these developmental changes decrease the chances that orbital roof hematomas will develop in adults (Tonna, 1974; Ma'luf et al., 2002; Augustin et al., 2007). The clinical finding that orbital roof subperiosteal hematomas are largely a childhood phenomenon is significant from a paleoepidemiological perspective; it in part explains the fact that "active" cribra orbitalia lesions are almost never found in adults.

Orbital lesions of this type are an especially common finding in scurvy cases (Dunnington, 1931; Ortner and Ericksen, 1997; Ortner et al., 1999; Ortner, 1999). Vitamin C deficiency weakens the Sharpey's fibers that attach the connective tissue covering the orbital roof. As a result, minor trauma associated with movements of the ocular muscles can result in detachment of the periosteum covering the orbital roof, subperiosteal bleeding, and subsequent formation of a layer of porous, highly vascular, subperiosteal new bone. If scurvy is chronic, repeated episodes of this same process can result in the buildup of layers of new bone in different stages of healing and thus produce major modifications of the orbital roof's thin outer table. These ocular complications were commonly seen in scurvy patients during the 19th century and are well described by Barlow (1894, p 1076): "The proptosis [bulging eyeballs] which occurs in the disease in question [scurvy] is caused by a blood extravasation into this easily distended space between the roof of the orbit and its periosteum. The eyeball is pushed downwards and forwards, and the upper lid becomes tense and bulged and sometimes a little discoloured."

People with these orbital lesions are very likely to have suffered from multiple nutritional deficiencies and this further complicates the differential diagnosis of cribra orbitalia. For example, during the 19th century, the common co-occurrence of rickets and scurvy in the same patients greatly hindered differential diagnosis of the two conditions (Cheadle, 1878; Barlow, 1883, 1894; Railton, 1894). This problem of identifying the effects of multiple nutritional deficiencies is made all the more difficult in the context of paleopathological studies where skeletal remains and their archaeological context are our only sources of evidence.

Whatever the causes of cribra orbitalia are, it seems clear that iron-deficiency anemia per se is not one of them. Of course, many, if not most people with cribra orbitalia may also have suffered from iron-deficiency anemia, but correlation is not causation. The evidence for a causal relationship between cribra orbitalia and iron-deficiency anemia suffers from the same problem as attempts to explain porotic hyperostosis as an iron-deficiency anemia response: iron-deficiency anemia does not stimulate the massive marrow hypertrophy necessary to produce these lesions.

A PUEBLOAN TEST CASE

In this article, we argue that porotic hyperostosis and many cribra orbitalia lesions are osseous responses to the megaloblastic anemia that nursing infants acquire from vitamin-B_{12}-deficient mothers. Such babies are born with low vitamin B_{12} reserves that are further depleted by the synergistic effects of low vitamin B_{12} concentrations in the mother's breast milk and unsanitary living conditions conducive to nutrient losses from gastrointestinal infections. If the maternal diet is vitamin B_{12} deficient, weaning foods are likely to be as well and this would further increase the risk of megaloblastic anemia (see Fig. 4).

The Ancestral Puebloans provide an ideal test case for this hypothesis. These predecessors of modern Pueblo groups such as the Hopi and Zuni tribes occupied the Colorado Plateau region. Much bioarchaeological work has been done to document the extremely high rates of porotic hyperostosis and cribra orbitalia among these Ancestral Puebloans (Zaino, 1967; El-Najjar et al., 1975; El-Najjar et al., 1976; Von Endt and Ortner, 1982; Berry, 1983; Hinkes, 1983; Walker, 1985; Palkovich, 1987; Martin, 1991; Tyson et al., 1999; Schultz and Schmidt-Schultz, 2002; Ortner, 2003; Stodder, 2006). For example, at Canyon de Chelly, 72% of the Basketmaker period and 88% of the Puebloan period children who died between the ages of 0–10 years exhibited porotic hyperostosis (El-Najjar et al., 1976). If infantile megaloblastic anemia is the principal cause of porotic hyperostosis and cribra orbitalia, we would expect to find evidence of vitamin-B_{12}-deficient diet and gastrointestinal infections among the Ancestral Puebloans (see Fig. 4).

The Puebloan diet

Archaeological evidence shows that the Ancestral Puebloans became increasingly maize dependent (Polyak and Asmerom, 2001; Benson et al., 2003). Concomitant with this agricultural intensification, overhunting of large game reduced their animal food access. These dietary changes varied regionally and did not involve simple unilinear processes. Multiple lines of evidence suggest at least three dietary change trajectories: 1) considerable early maize use followed by increasing dependence, 2) initial heavy use with little later increase, and 3) minor use for long periods followed by much greater later dependence (Hard et al., 1996). Isotopic studies and other independent lines of evidence indicate that by the time of European contact, 70–90% of the calories in the diets of most Ancestral Puebloans were derived from maize (Decker and Tieszen, 1989; Spielmann et al., 1990).

Dental caries rates, which tend to increase with the consumption of carbohydrate-rich cultigens (Walker and Erlandson, 1986; Walker and Hewlett, 1990; Larsen, 1995), reinforce this picture of a complex pattern of dietary change. Schollmeyer and Turner (2004) found high caries rates consistent with heavy maize dependence among both the earlier Basketmaker and later post-Basketmaker groups they studied. However, during post-Basketmaker times carious surfaces between the teeth increase significantly. This probably reflects more intensive milling: a labor-intensive strategy for increasing the nutritional value of maize by grinding it into finer, stickier, easily digestible particles that tend to lodge between the teeth and produce caries (Hard et al., 1996; Schollmeyer and Turner, 2004).

Most of the time, the Ancestral Puebloan diet appears to have been nutritionally adequate (Cummings, 1994). Labor-intensive harvesting of small, hard seeds (e.g. amaranth and chenopodium) continued to supplement the

maize-based diets throughout the period of agricultural intensification (Whalen, 1981; Wills, 2001; Adams and Fish, 2006). Coprolite studies show that people were sometimes also able to supplement their diets with nutritious pollen-rich foods (Reinhard et al., 2006) and insects (Moore et al., 1969; Rohn, 1971).

Starvation from drought-induced crop failures, however, was clearly an ever-present threat. By far, the most common themes in Hopi legends, myths, and folktales are issues surrounding drought, famine, crop failure, and concerns about crop success (Voth, 1905; Brandt, 1954). For example, Curtis (1922) recounts a famine among the Hopi in which "dry cactus fruit and grass seeds were gathered, and when these failed the starvlings prowled among the neighboring ruins and dug in the piles of refuse for old bones, which they boiled. Women would snatch the last grain from their weeping children, and some cases of cannibalism occurred" (also see Cushing, 1920; Curtis, 1922). Such stories persist in Hopi oral history. The mother of one of Brandt's consultants explained that during the times of famine "the Hopi gave their children nothing to eat. There was only enough for a man and his wife. You had to save your own life. Children aren't worth it to you when starvation comes; it's all for yourself and your wife" (Brandt, 1954, p 192). Social unrest and the execution of witches accused of engaging in anthropophagy during times of drought and disaster are also well documented Puebloan oral history themes (Goldfrank, 1945; Darling, 1998; Malotki and Gary, 1999).

Studies of Puebloan skeletal remains also suggest that nutritional shortfalls were common. Not only are cribra orbitalia and porotic hyperostosis frequent findings, but there are other osteological indications of nutritional deficiency. Examination of a large Puebloan skeletal series revealed evidence of scurvy in 2.7% of the subadult skeletons examined (Ortner et al., 2001). This is consistent with the famine-induced scurvy outbreaks seen among marginal agriculturalists living in drought-prone, arid and semiarid environments similar to those in the Puebloan area. Among the Tswana speaking people of Botswana, for example, scurvy was a recurrent drought-induced health problem during the 19th and early 20th centuries (Wylie, 1989).

Resource depletion

Overexploitation of local plant and animal resources had significant nutritional consequences for the Ancestral Puebloans that help explain the prevalence of porotic hyperostosis and cribra orbitalia among them. Farming and intensive fuel wood harvesting at Mesa Verde and other parts of the Puebloan region markedly altered the local landscape through woodland reduction (Kohler and Matthews, 1988; Dean, 2004). In hearth samples from the Mimbres area, decreases in riparian species and increases in pollen from disturbance-loving plant species suggest substantial land clearing for field and village expansion (Minnis, 1978; Nelson and Schollmeyer, 2003). In the Dolores area, increases in maize production are paralleled by a decline in piñon trees, whose nuts were a valuable protein source. The wood from these trees was undoubtedly used for construction and as fuel (Kohler, 1992). Similar changes occurred at Chaco Canyon sites in northwestern New Mexico where the sparse piñon-juniper woodland that once surrounded the canyon appears to have been destroyed through fuel wood harvesting (Samuels and Betancourt, 1982).

These decreases in the availability of wood for heating, cooking, and construction purposes had important nutritional consequences. Difficulties in obtaining wood for heating homes would significantly increase winter caloric requirements. Cooking can greatly increase the nutritional value of both plant foods and meat (Stahl, 1989; Crown and Wills, 1995; Wrangham et al., 1999; Wrangham and Conklin-Brittain, 2003; Boback et al., 2007). Problems obtaining fuel for cooking would thus have negative nutritional consequences throughout the year. As local firewood sources were depleted, meeting these critical heating and cooking needs would require more and more time and energy investments in obtaining fuel wood from increasingly distant sources.

These anthropogenic changes in local plant communities were accompanied by the depletion of wild game. Loss of this valuable vitamin B_{12} source would greatly increase the risk of megaloblastic anemia. Throughout the Puebloan region, the proportion of large game animals, primarily deer and pronghorn, in archaeological trash middens tends to decline through time while the proportion of small game (mainly rabbits) and domestic turkeys increases (Stiger, 1979; Seme, 1984; Szuter and Bayham, 1989; James, 1990; Olsen, 1990; Munro, 1994; Sanchez, 1996; Spielmann and Angstadt-Leto, 1996; Cannon, 2000; Varien et al., 2000; Rawlings, 2006). This dietary shift toward small game and domestic turkey is consistent with the vulnerability of large, slowly reproducing mammals to overhunting (Kohler and Van West, 1996; Wills, 2001). The loss of large game would be significant because of the high nutrient returns they provide per unit hunting effort (Gurven and Hill, 2006). This loss was mitigated to some extent by turkey raising, a practice that had its own health-related costs.

Early historical accounts provided by Spanish explorers in the American Southwest document the domestication, penning, and herding of turkeys (*Meleagris gallopavo*) on a large scale (Winship et al., 1904). Intensive turkey use by some earlier Puebloan groups is also well documented through zooarchaeological studies (Beacham and Durand, 2007; Munro, 2006). Turkey remains are especially common in faunal collections from the Four Corners area where the archaeological evidence suggests that dependence on turkeys for meat, eggs, and feathers gradually increased through time (Durand, 2006; Munro, 2006; Beacham and Durand, 2007).

After AD 1100, there is a noticeable increase in turkey remains across the northern Southwest in the Chaco and Mesa Verde regions as well as elsewhere in the Puebloan region (Beacham and Durand, 2007). The frequency of turkey bones rose steadily in the northern San Juan region, and reached 17% of the total fauna at Pueblo Alto in Chaco Canyon (Windes, 1987). The trend toward intensified turkey production peaked in the Mesa Verde region where turkey remains make up as much as 69% of the faunal assemblages at some Pueblo III sites (Munro, 1994; Muir and Driver, 2002; Munro, 2006).

This emphasis on turkey husbandry was likely a response to nutritional problems associated with the increased maize dependence and depression of local wild animal resources that occurred with population aggregation in large settlements. Although rich in carbohydrates, maize is deficient in protein, essential minerals, such as iron, and vitamins (Spielmann and Angstadt-Leto, 1996). In the context of depleted wild animal protein sources, turkey husbandry would provide a cost-effective source of animal protein and other essential nutrients such as

vitamin B_{12} (Munro, 2006; Spielmann and Angstadt-Leto, 1996).

Although turkeys were valuable a food source, raising them in the crowded setting of Puebloan villages would pose its own health hazards. Once habituated to humans, it is very difficult to keep turkeys and their fecal material away from dwellings (Pinkley, 1965). This is attested to by the deep deposits of turkey dung archaeologists have occasionally found surrounding Puebloan homes (Rohn, 1971; Rohn, 1977). Through the contamination of food and water, this would create an ideal environment for the spread of enteric bacteria such as *Salmonella* and *Shigella* that cause diarrheal infections (Kunitz, 1969; Kunitz and Euler, 1972; Kent, 1986; Beli et al., 2001).

Sanitation problems

Sanitation problems such as those associated with raising turkey are likely to have contributed significantly to the prevalence of porotic hyperostosis and cribra orbitalia among the Ancestral Puebloans. A diet deficient in vitamin-B_{12}-rich animal foods would have interacted synergistically with nutrient losses from parasite infections spread by poor sanitation to produce vitamin B_{12} deficiencies in mothers who would in turn transmit this deficiency in an accentuated form to their nursing infants (see Fig. 4). Such deficiencies would be exacerbated if the infant, mother, or both contracted diarrheal disease from contaminated food and water.

Diarrheal disease was a major health problem for Puebloan people during the first part of the 20th century before plumbing for indoor water and toilets became available (Aberle, 1932; Lasersohn, 1965; Rubenstein et al., 1969). Aberle (1932) documented high infant mortality rates from gastrointestinal infections at two Tanoan Pueblos and attributed this in part to poor hygiene. It was observed that "infants are seldom bathed, and no attention is paid to cleanliness of mouth, ears, or nose." Aberle also noted that some of the Puebloans parents he worked with viewed what he considered serious gastrointestinal problems as commonplace occurrences unworthy of a doctor's attention (Aberle, 1932, p 341).

Colton (1936; 1960) argued that poor sanitation was a major cause of disease in the larger Pueblo villages and observed that "the excreta are often deposited in the narrow plazas, streets, middens, and passages near the houses" where they contaminate drinking water (Colton, 1960, p 113). He also noted the health hazards posed by this excrement-contaminated environment increased when it rained: "Although the drinking water is usually procured from a spring at some distance from the village, yet in times of heavy rainfall, temporary pools form on the rocks close to the village which are filled by surface runoff. This water is contaminated from excreta. When one protests to a Hopi grandmother about giving an infant a drink from the pool in the street, she says that the water can't be bad because it fell from the clouds and so was especially sent by the Heavenly God" (Colton, 1936, p 342). Colton goes on to note that, because of this water contamination problem, infant mortality of the Hopi children less than 2 years of age after the summer rainy season is very great. Lasersohn (1965) documented a similar seasonal pattern among the Zuni, with a late summer peak in reported cases of diarrheal disease.

There is ample documentation of unsanitary living conditions at Puebloan villages during the late 19th and early 20th centuries. Donaldson gave a first-person description of a Hopi village in 1890: "the Moqui pueblos ... are now generally a mass of filth and dirt, the accumulation of ages. The streets in some are many feet above the level of the town and houses, and you now 'go down into' in entering a house, the 'building up' being offal and vile refuse" (Donaldson, 1893, p 6). According to Titiev (1944, p 205), at Orayvi "Toilet facilities are completely wanting, and but little trouble is taken to conceal the performance of the natural offices. Men and boys especially, urinate at will ..." (also see: Beaglehole, 1935; Talayesva, 1963).

Ethnohistorical and archaeological data suggest that earlier Puebloan communities varied considerably in their waste disposal and sanitation practices. Castaneda, the chronicler of the Coronado expedition, described Pueblo villages as "free of nuisances, because they go outside to excrete, and they pass their water into clay vessels, which they empty at a distance from the village" (Winship et al., 1904, p 100). On the other hand, archaeologists have occasionally documented large quantities of fecal material at some Ancestral Puebloan sites (Graham, 1965). Waste disposal practices and the health hazards they posed clearly varied through time and between villages. As Reinhard (1988) notes, the random excreta disposal pattern of the Antelope House inhabitants and the propensity of the people of this village to forage in wetter areas put them at a much higher risk of helminth infection than the inhabitants of Salmon Ruin, who established latrines and foraged in dryer woodlands. Local topography is also an important consideration: at some cliff dwellings, excreta could be easily thrown into ravines where the risk of water contamination was minimal (e.g., Curtis, 1922). At other villages, especially those in canyon bottoms, waste disposal would be much more problematic (Walker, 1985).

Paleopathological studies of coprolites have shown that *Giardia lamblia* afflicted some Ancestral Puebloans (Carvalho Gonçalves et al., 2003). This common waterborne pathogen causes chronic diarrhea, malabsorption of nutrients, and B_{12} deficiency, especially in individuals who are already nutritionally compromised (Olivares et al., 2002). We know from coprolite studies that Ancestral Puebloans also had helminth infections that would have contributed to anemia (Reinhard et al., 1987). Pin worms are present in desiccated human fecal material from a number of dry caves in the Southwest (Samuels, 1965; Fry and Moore, 1969; Reinhard et al., 1985; Reinhard and Hevly, 1991; Carvalho Gonçalves et al., 2003) and tapeworms are present in material from a Glen Canyon Anasazi site (Fry, 1977). Although pinworms and most tapeworm species are relatively benign, they can stimulate a low-grade eosinophilia (Leder and Weller, 2000). Spinyheaded worms would have presented a much more serious health hazard. The eggs of this helminth were recovered from coprolites excavated at Danger Cave (Moore et al., 1969) and Glen Canyon (Fry, 1977). These people were probably infected through eating the insects that are intermediate hosts for the parasite (Moore et al., 1969).

Social inequalities in food access

Social factors appear to have resulted in unequal access to animal foods both within and between Ancestral Puebloan communities and this would have exacerbated the nutritional problems faced by some people. Faunal studies suggest that people living in larger communities were able to obtain more meat from deer and

other artiodactyls than those living in smaller settlements. The distribution of artiodactyl, wild bird, and rabbit bones within large settlements indicate that people living in roomblocks with distinctive architectural features had more meat access than people with more pedestrian quarters (Muir and Driver, 2002).

Bone chemistry studies provide substantial evidence of socially mediated nutritional inequalities among ancient Native Americans in the Puebloan region. At Pueblo Grande, a Hohokam site, it appears that males consumed a greater proportion of the available meat than females (Sheridan, 2001; Sheridan, 2003). Bone chemistry studies suggest that at Grasshopper Pueblo, the residents of one part of the village ate more meat than others (Ezzo, 1994; Ezzo, 1993); similar dietary differences may also have existed among females buried at the NAN Ranch site (Holliday, 1996).

Ethnographic reports substantiate the existence of social inequalities with significant health consequences that are reflected in clan differences in fertility and longevity (Levy, 1992). At the Hopi village of Orayvi on Third Mesa, clans were assigned fields by the village chief. Some clans received excellent fields and others less desirable pieces of land or nothing at all (Levy, 1992). In times of drought all resources were "concentrated for the preservation of the central clan core, and other clansmen may be forced to migrate or starve. As conditions improve, they may return . . ." (Eggan, 1966, p 125). A major "sloughing off" of clans occurred in 1906 when a prolonged drought caused half the Orayvi population, consisting mostly of lower class Hopi, to be expelled from the village and prevented from returning (Levy, 1992).

There are indications that the drought-induced food shortages accentuated such social inequalities and led to warfare and violence. This would further increase the nutritional problems these people faced through diversion of resources away from food production toward defensive purposes. For example, a well-documented outbreak of violence occurred between A.D. 1150 and 1250. During this period, considerable investments were made in the construction of dwellings within enclosing walls and masonry towers in easily defended locations (Kenzle, 1997; Kohler et al., 2008; LeBlanc, 1999). The proximate cause of the collapse of the Canyon political system at this time and the stimulus for an outbreak of intense interpersonal violence around A.D. 1150 appear to have been a severe, prolonged, tree-ring-documented drought that occurred between A.D. 1135 and 1170 (Benson et al., 2007; Dean, 1992:40; Kohler et al., 2008). Analysis of skeletal collections from the Mesa Verde region indicates a sharp increase in anthropophagy around A.D. 1150, a phenomenon that has been interpreted as a response to the drought-induced heightened resource competition and the collapse of intercommunity alliances that had previously maintained peace (Billman et al., 2000; Marlar et al., 2000; White, 1992).

Raiding for women and children is ethnohistorically well documented in the American Southwest during the early historic period (Brooks, 2002) and there is paleodemographic evidence that suggests it also occurred in ancient times (Kohler and Turner, 2006). Paleodemographic data suggest that by the thirteenth century, if not earlier, raiding for women was common in some areas of the Puebloan region (Kohler and Turner, 2006; Martin et al., 2001). The enslaved victims of such raids would most likely have low status in the communities they were brought to; as a result, it is unlikely that these women would receive highly desirable animal foods during times of scarcity. This in turn would greatly increase the likelihood that their babies would suffer from the nutritional deficiencies we have linked to porotic hyperostosis.

CONCLUSIONS

In this article, we have shown that iron-deficiency anemia does not provide a reasonable physiological explanation for the marrow hypertrophy that produces the pathological lesions paleopathologists refer to as porotic hyperostosis and cribra orbitalia. Humans respond to iron-deficiency anemia by restricting RBC production rather than increasing it. As a result, iron-deficiency anemia cannot logically be considered the cause of the marrow expansion that produces porotic hyperostosis and some forms of cribra orbitalia.

We argue that porotic hyperostosis and many cribra orbitalia lesions are a result of the megaloblastic anemia acquired by nursing infants through the synergistic effects of depleted maternal vitamin B_{12} reserves and unsanitary living conditions that are conducive to additional nutrient losses from gastrointestinal infections around the time of weaning (see Fig. 4). The lesions paleopathologists identify as cribra orbitalia can be attributed to a greater range of causes than porotic hyperostosis, and we argue here that subperiosteal bleeding associated with a codeficiency of vitamin C and B_{12} combine to explain the presence of the condition in Ancestral Puebloan populations.

Reconsidering the etiology of porotic hyperostosis and cribra orbitalia has important implications for current interpretations of malnutrition and infectious disease in earlier human populations. Although these skeletal conditions may often be associated with iron-deficiency anemia, we have shown that iron-deficiency cannot be their cause. The hematological evidence we have presented instead suggests that a vitamin-B_{12}-deficient diet is much more likely to be the key nutritional component in the set of interacting variables responsible for both porotic hyperostosis and many cases of cribra orbitalia.

Our explanation of these conditions focuses on the clinically well-documented effects that vitamin-B_{12}-deficient maternal diets lacking foods of animal origin have on nursing infants. The clinical studies we cite show that modern children whose parents, for ideological reasons, strictly avoid the consumption of all animal products may develop severe cases of megaloblastic anemia if they do not artificially supplement their diets with vitamin B_{12}. Under the unsanitary living conditions of many earlier human populations, such infantile deficiencies would be increased further by nutrient losses associated with the diarrheal diseases that cause high rates of infant mortality under such circumstances. As the Ancestral Puebloan example we have given shows, such problems would be even more prevalent during drought-induced periods of warfare, famine, and socioeconomic collapse (see Fig. 4).

The Ancient Puebloans also show that such conditions could easily arise among New World agriculturalists lacking foods of animal origin, living in marginal, drought-prone environments in which wild game are easily depleted. Under such conditions, over-exploitation of local animal resources can reach a point where socially disadvantaged people become obligatory vegetarians. Access to animal resources would be further restricted during times of warfare and social unrest

because normal hunting and gathering activities are often infeasible during such dangerous times. Aggregation for defensive purpose would pose additional problems of sanitation, water contamination, and enhanced parasite transmission rates that would further deplete the nutritional stores of affected individuals. Under such conditions, the nutritional deficiencies suffered by mothers would be transmitted to their infants in an exacerbated form (see Fig. 4).

There is considerable evidence that each of these problems did exist at times among the Ancestral Puebloans. These Puebloan data are thus consistent with the causes we have proposed for porotic hyperostosis and cribra orbitalia. In this regard, it is relevant to note the virtual absence of porotic hyperostosis in many ancient European populations living outside of regions where malaria-related hemolytic anemias are a health hazard. In light of the etiology we have proposed for porotic hyperostosis, this is easily explained by the fact that the modest quantities of meat and dairy products available to these Europeans who practiced both agriculture and animal husbandry would have contained sufficient vitamin B_{12} to prevent severe cases of infantile megaloblastic anemia. This reasoning also leads to the conclusion that the cribra orbitalia that is common in some northern European populations is more likely to be a result of scurvy, or chronic infections such as those associated with trachoma (e.g., Webb, 1990), than it is of vitamin B_{12} deficiency.

If we are correct in our conclusion that vitamin B_{12} deficiency is an important element in the complex set of synergistic factors predisposing infants to develop porotic hyperostosis and cribra orbitalia, this has some interesting behavioral implications. Not only does vitamin B_{12} deficiency produce megaloblastic anemia, but it also is associated with debilitating neurological problems including paranoia, depression, mania, psychosis, and dementia (Hart and McCurdy, 1971; Zucker et al., 1981; Hector and Burton, 1988; Berry et al., 2003; Durand et al., 2003). It is at least worth considering the possibility that such neurological problems contributed to the outbreaks of interpersonal violence and anthropophagy that erupted among the Ancestral Puebloans during and subsequent to the well-documented drought that occurred in the American Southwest between A.D. 1135 and 1170.

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