The Role of Constitutional Factors, Diet, and Infectious Disease in the Etiology of Porotic Hyperostosis and Periosteal Reactions in Prehistoric Infants and Children

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ABSTRACT. A model of analysis incorporating methodological improvements and epidemiological refinements has been employed to investigate the etiology of porotic hyperostosis and periosteal reactions in infants and children from the Libben Site, a Late Woodland ossuary and occupation site from Ottawa County, Ohio. Results of the age-specific intrapopulational analysis of porotic hyperostosis demonstrate that the skeletal lesion strongly fits the age-specific distribution of hypochromic microcytic iron-deficiency anemia in infants and children. The data indicate that the lesion is a response to nutritional stress. Similarly, our findings show that the age-specific distribution of periosteal reactions strongly...

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coincides with, and appears to be a response to, infectious disease as it occurs in infants and children. More importantly, survivorship and growth data indicate that porotic hyperostosis and periosteal reactions are strongly associated with patterns of infant and child morbidity and mortality, and therefore appear to play an important role in selection and fitness at Libben. Based upon the age-specific patterns and associations observed for porotic hyperostosis and periosteal reactions in the Libben infants and children, it is suggested that:

1) the current methodological procedure of partitioning skeletal populations into broad age categories can significantly distort important age-specific pathophysiological relationships;  
2) skeletal lesions should be classified according to their physical quality (i.e., remodeled and unremodeled) to provide an estimate of both the morbidity and mortality associated with the age-specific distribution of a particular skeletal lesion;  
3) porotic hyperostosis may be a valuable indicator of nutritional stress which can be employed to evaluate the nutritional status of prehistoric human populations;  
4) the pathogenesis of porotic hyperostosis can best be understood in terms of the synergistic interactions between constitutional factors, diet, and infectious disease.

The study of human paleopathology is concerned with disease process as a selective agent in the evolutionary history of our species. As an evolutionary biologist, the paleopathologist attempts to describe, to classify, and to interpret the epidemiological parameters of disease in human populations. The objectives of such studies should be twofold: first, to employ disease patterns to evaluate the relative fitness of a human population under stress; and second, to analyze the interactions among cultural, biological, and environmental components of disease process as they contribute to the nature and scope of human variation.

Patterns of infant and child morbidity and mortality are among the most useful parameters of population pathology which are available to the paleoepidemiologist. Well-documented epidemiological studies have demonstrated that infant mortality has such a profound influence on the crude death rate of a population, that it has become accepted as a measure of population fitness (Gordon et al. 1967). In addition, both clinical and epidemiological research have demonstrated that patterns of infant and child morbidity and mortality are strongly associated with the synergistic interactions between nutritional deficiencies and infectious disease (Gordon et al. 1963, 1967; Scrimshaw and Suskind 1959).

Unfortunately, the analysis and interpretation of disease processes in earlier human populations are often compromised by the condition of the skeletal materials, and by the methods used in the analysis of these materials (Carlson et al. 1974). A particularly important problem is related to the differential preservation of skeletal materials. Both the degree of skeletal completeness, and the state of preservation can strongly influence the reliability and validity of paleodemographic data by skewing survivorship curves and life expectancy estimates of the sample. Similarly, poor sampling of subadult specimens, and small samples in general, can lead the researcher to use gross statistical lumping procedures which may obscure important age-specific patterns of stress, and make it difficult to apply the comparative method to further research. It is important to realize that paleoepidemiologic analysis can easily become an exercise in sampling error.

In order to deal with these problems the present study has incorporated methodological improvements and paleoepidemiological refinements into a stress model designed to investigate infant and child morbidity and mortality in prehistoric human populations. The methodological improvements are concerned with techniques for sampling and aging subadult skeletal material. The paleoepidemiological refinements focus on the intrapopulational analysis of age-specific patterns in disease processes. The purpose of this study is to examine the synergistic interaction between nutritional deficiency and infectious disease, and to relate this interaction to the etiology of two classes of nonspecific skeletal lesions. These lesions are porotic hyperostosis and periosteal reactions.
POROTIC HYPEROSTOSIS

Porotic hyperostosis is a descriptive term referring to cranial lesions which affect the anterior portion of the supraorbital plate, and the pericranial surfaces of the frontal, parietal, and occipital bones (Angel 1966). The temporal, sphenoid, and facial bones are less frequently involved. The lesion characteristically exhibits a coral, cribiform, or sieve-like porosity with marginal hypervascularity (Moseley 1965). More severe manifestations of the lesion display a symmetrical "spongy bone" appearance which is due to excessive tissue hypertrophy and obliteration of the outer table. Radiologic and histologic studies (El-Najjar and Robertson 1976a; Moseley 1965) demonstrate that the lesion usually displays a widening of the diploic spaces, irregular trabeculation, thinning of the tables (primarily the outer table), and a radial pattern of bone spiculation known as "hair-on-end" striations. These striations usually occur perpendicularly to the endocranial table.

The structural alterations observed in porotic hyperostosis are known to occur in a number of disease processes (Table 1). These alterations of bony structure are commonly observed in chronic hemolytic anemia (Baker 1964; Caffey 1937; Moseley 1974; Sheldon 1936; Williams et al. 1975); and in iron-deficiency anemia (Agarwal 1970; Askoy et al. 1966; Britton et al. 1960; Burko et al. 1961; Eng 1958; Lanzowsky 1968; Powell et al. 1965; Sax 1963; Shahidi and Diamond 1960). The lesions are less frequently observed in cyanotic congenital heart disease (Nice 1964); in hereditary spherocytosis (Trucco and Brown 1967); in polycythemia vera (Dykstra and Halberstma 1940); and in pyruvate kinase deficiency (Becker et al. 1971). The skeletal changes which resemble porotic hyperostosis in all of these conditions are due to erythroid marrow hyperplasia in response to an underlying anemic stimulus (Moseley 1974). The lesions should therefore be considered a nonspecific consequence of bone marrow proliferation.

The earlier medical and anthropological reports on porotic hyperostosis were published under a variety of descriptive terms and were accompanied by a variety of proposed etiologies. The

Figure 1. Burial 08027, 7-8 year old child with bilateral porotic hyperostosis of the orbits.

Figure 2. Burial 04035, 12-18 month old infant displaying spongy hyperostosis of the right parietal bone.
more common referents included cribra orbitalia (Welcker 1888); symmetrical osteoporosis (Hrdlicka 1913; Williams 1929); osteoporosis of the cranium (Muller 1935); cribra cranii (Henschel 1961); and spongy hyperostosis (Putschar 1966). In general, these studies have demonstrated that the lesion has a widespread geographical distribution, and that it occurs with the highest frequencies in equatorial regions. Several of the most recent studies have suggested two primary explanations of the etiology and distribution of porotic hyperostosis in prehistoric skeletal populations.

One hypothesis suggests that porotic hyperostosis is the result of a hemolytic anemia resulting from a balanced polymorphic adaptation to falciparum malaria (Angel 1964, 1966, 1967). The temporal and geographical distributions of the lesion in many areas of the Old World fit this hypothesis well. The second explanation is that porotic hyperostosis results from a chronic iron-deficiency anemia (Carlson et al. 1974; El-Najjar et al. 1976a; Hengen 1971; Lallo et al. 1977). Evidence favoring the latter hypothesis includes the following: 1) iron-deficiency anemia is the most prevalent nutritional deficiency throughout the world (Robbins 1974), and porotic hyperostosis, likewise, has a widespread distribution both in the Old World and in the New World (El-Najjar et al. 1976b; Hengen 1971); 2) the frequency distribution of porotic hyperostosis corresponds well with the distribution of dietary staples characterized by foodstuffs low in bioavailable iron (Carlson et al. 1974; El-Najjar et al. 1976b); and 3) at present, there is no reliable evidence to suggest that any of the hemolytic anemias associated with the skeletal changes observed in porotic hyperostosis in the Old World were operative as a selective factor in the pre-Columbian New World (El-Najjar et al. 1976c; Steinbock 1977).
PERIOSTEAL REACTIONS

Periosteal reactions is another type of nonspecific skeletal lesion which occurs in association with a wide variety of pathological conditions. Commonly referred to as periosteal elevations or periostitis, this lesion is most frequently found on the shafts of long bones but can also occur on the orbital, endocranial, and ectocranial tables. Periosteal reactions commonly occur in a number of disease conditions (Greenfield 1975), some of which are summarized in Table 2.

Table 2.  Partial list of conditions creating Periosteal Elevation.*

1. Benign Conditions Characterized By Generalized Periosteal Elevation
   1. Pulmonary Hypertrophic Osteoarthropathy
   2. Thyroid Acropachy
   3. Pachydermoperiostosis
   4. Infantile Cortical Hyperostosis
   5. Hypervitaminosis A

II. Other Benign Conditions Commonly Associated With Generalized Periosteal Elevation
   1. Prematurity
   2. Venous Stasis
   3. Subacute Lupus Erythematosus (arteritis)
   4. Polyarteritis Nodosas
   5. Rheumatoid Arthritis
   6. Reiter’s Syndrome
   7. Psoriatic Arthritis
   8. Battered Child Syndrome
   9. Thermal Injuries
   10. Widespread Osteomyelitis
   11. Widespread Infarcts Of Bone (especially hand-foot syndrome in sickle cell anemia)
   12. Rubella
   13. Scurvy
   14. Healing Nickets
   15. Infantile Hurler’s Syndrome
   16. Caucher’s Disease
   17. Histiocytosis X
   18. Myeloclesrosis
   19. Fluorosis
   20. Cornelia de Lange Syndrome II(pseudomuscular hypertrophy)
   21. Idiopathic


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Periosteal reactions are usually manifested grossly as a smooth, irregular, or spiculated new layers of bone which appear as a “scab” over the normal cortex (Figs. 4a, 4b, 4c, and 4d). More severe involvements exhibit serial layers of new bone that can envelope the entire bone and distort its normal contours (Moseley 1974). Radiologically (Fig. 5) periosteal reactions exhibit a solid, laminated, or spiculated pattern (Greenfield 1975). The lesion is often erroneously equated with osteomyelitis because the hematogenous spread of the microorganisms (staphylococcus and streptococcus) to bone tissue usually involves bone marrow (osteomyelitis), cortex (ostitis), and periostium (periostitis) in a systemic disease process (Jaffe 1972).

Periosteal reactions usually result from an elevation of the fibrous outer layer of the periostium because of blood vessels compressing and stretching (Jaffe 1972). A subperiosteal hemorrhage then occurs which reduces the blood supply to the bone. Any agent such as blood, pus, granulation tissue, neoplasm, or trauma may stimulate the reaction which can then impair normal cortical metabolism and result in necrosis. If the periostium is not destroyed, the cambium layer will resume osteoblastic activity and produce new subperiosteal bone.

Figure 4a. Burial OS076b, 6-12 month infant with chronic periostitis. Note the “scab” appearance of the subperiosteal bone deposition over the normal cortex of the tibial fragments.
Figure 4b. Burial 05208, 11-12 month infant with periositis along the medial border of the diaphysis of this tibial cross-section.

Figure 4c. Burial 01216, 7-8 month old specimen displaying a periossteal reaction on the endocranial aspect of a parietal fragment. Note the irregular appearance of the bone forming a “scab” over the normal endocranial table.

Figure 4d. Burial 01216, 7-8 month old infant which manifests a periossteal reaction affecting the posterior portion of the right orbit.

Figure 5. Burial 05076b, x-ray of humerus, tibia, and fibula fragments of a 6-12 month old specimen displaying the laminated pattern of new subperiossteal bone deposition.
It has been demonstrated that periosteal reactions frequently occur in skeletal collections, and that localized periosteal elevations are a common response of bone to overlying soft tissue infections (Morse 1969). Furthermore, periosteal reactions, which are believed to be the result of chronic infection, are commonly found in association with porotic hyperostosis (Lallo et al. 1977). Therefore the synergistic relationships between the two types of skeletal lesions may have important implications for patterns of infant and child morbidity and mortality.

In general, patterns of infant mortality exhibit consistent age-specific relationships with infectious disease. Gordon and co-workers (1967) have described three important stress-related periods for the neonatal and postnatal infant. The first is from birth to one month. The leading causes of death in this period are prematurity, birth injuries, congenital anomalies, asphyxia, atelectasis, and immediately acquired infections. The second period is from one to twelve months. The leading causes of death in this age class are infectious diseases such as bronchitis, pneumonia, otitis media, and gastroenteritis. The third period is from one to four years of age during which the frequency of malnutrition increases as the frequency of infectious disease begins to decrease.

The critical period for the infant in terms of the synergistic stresses imposed by nutritional deficiency and infectious disease is six to 24 months (Gordon et al. 1967). It is during this time that both malnutrition and infectious disease have their greatest impact on levels of infant and child morbidity and mortality in a population. Therefore, we are suggesting that the age-specific patterns of iron-deficiency anemia and infectious disease are of value to the paleopathologist concerned with the pathogenesis of porotic hyperostosis and periosteal reactions, and their roles as selective factors in prehistoric populations.

**HYPOCHROMIC MICROCYTIC IRON DEFICIENCY ANEMIA**

Modern epidemiological studies demonstrate that iron-deficiency anemia is so prevalent throughout the world that it is now regarded as an excellent index of the nutritional health of a population (Kilpatrick 1970; Wits 1966). Furthermore, clinical and experimental studies have documented consistent age- and sex-specific risk factors in the etiology of iron-deficiency anemia (Hallberg et al. 1970; Heath and Patek 1937). The more important risk factors are rate of growth, which primarily affects infants and adolescents, and physiological blood loss, due to the onset of menstruation in adolescent females or to menstruation and pregnancy in adult females. Infants and children in particular can exhibit an age-specific syndrome referred to as hypochromic microcytic iron-deficiency anemia (Josephs 1956; Smith 1954).

The hypochromic microcytic iron-deficiency anemia in infants and children is a well studied syndrome which has a worldwide distribution (Finch 1968a, 1968b; Josephs 1953; WHO 1968). Clinical manifestations include erythroid marrow hyperplasia, reduced serum iron, and elevated latent iron-binding capacity of the serum (Smith 1972). The anemia commonly affects infants between the ages of 6 to 24 months (Heath and Patek 1937; Smith 1954). In premature and low birthweight infants the anemia occurs at an earlier age and is more pronounced (Reedy et al. 1952; Schulman 1959). In contrast to the iron-deficiency anemia of adults, the anemia of infants is only moderately responsive to iron therapy (Brozovic 1974; James and Combes 1960; Schulman et al. 1954), rarely produces tissue changes such as atrophic glossitis, dysphagia, or spoon-shaped nails (Smith 1972), and usually disappears spontaneously between the ages of two and three years (Josephs 1956).

In modern societies, pediatricians and clinical researchers often consider the anemia of infants to be a physiological condition in which the child is more anemic than clinically ill (Betke 1970; Sturgeon 1956). In developing countries, however, the condition is typically more severe and contributes significantly to patterns of infant and child morbidity and mortality (Akel et al. 1963; Ashworth 1973; Burks et al. 1976; Grantham-McGregor et al. 1974; Manchandra et al. 1969).

It is well recognized that the pathogenesis of the hypochromic microcytic iron-deficiency anemia in infants can rarely be
attributed to a single factor (Dawson and Desforges 1958; Davidson et al. 1935; Heath and Patek 1937; Mackay 1931). Constitutional factors such as iron stores at birth, birthweight, and rate of growth can precondition the infant to a borderline nutritional status (Josephs 1956). In addition, the process of weaning can generate a prolonged dependence on foods low in bioavailable iron such as milk, unfortified cereals, and carbohydrates. All of these foodstuffs can contribute to poor iron retention diets (Heath and Patek 1937; Josephs 1953). Also, the high frequency of respiratory and gastrointestinal infections which are so common among infants and children dramatically affect the bioavailability of iron, and the biological resistance of the host (Scrimshaw 1964). A brief discussion of constitutional factors, diet, and infectious disease will demonstrate the nature of their synergistic interactions, and their potential role in the etiology of porotic hyperostosis and periosteal reactions.

Iron Stores at Birth

Both prenatal and postnatal events are involved in the iron economy of the infant for the first six months of life. The prenatal factors affecting iron stores include: length of gestation; material iron deficiency; and hemorrhage (Smith 1972). The most important prenatal variable is length of gestation—events such as prematurity, twinning, and multiple births reduce the quantity of iron available to the neonate (Woodruff 1958). Maternal iron deficiency is reported to have only a slight effect on the hemoglobin level of the infant at the end of the first year of life (Woodruff and Bridgeforth 1953), and is not considered to be a major epidemiological variable in anemia. Similarly, placental hemorrhage can reduce iron stores at birth; however, it is relatively infrequent (Smith 1972).

At birth, both full-term and pre-term infants are born with iron concentrations relatively proportional to body weight (Mackay 1931). From about nine days to two months, all infants experience a normochromic normocytic anemia which is extremely important in relation to the infant’s iron economy for the first six months of life (Smith 1972). The phenomenon is referred to as the “physiologic anemia of infancy,” and is considered a fundamental adaptation to the extrauterine environment (Gairdner et al. 1952). Prior to birth, erythropoiesis in the fetus is very active in response to the relatively hypoxic intrauterine environment (Haavardsholm Finne and Halvorsen 1972). At birth, the lungs replace the placenta as the source of oxygen and the arterial saturation rises dramatically from 45 to 95% (O’Brien and Pearson 1971). The body responds to this abrupt change by depressing erythropoiesis. As circulating erythrocytes expire and body size increases, hemoglobin level declines. The three most important factors involved in these physiological adjustments are depressed erythropoiesis, hemodilution, and hemolysis (O’Brien and Pearson 1971). The iron released from the destruction of red blood cells during the first two months of life is the primary source of hemoglobin for the first six months of life, or until this source is depleted by rapid growth (Josephs 1956; Smith 1972).

Birthweight and Rate of Growth

Premature and low birthweight infants experience an early iron-deficiency anemia which begins at two months and usually lasts until about nine months of age (Gairdner et al. 1955; Merritt and Davidson 1934). This is clinically referred to as the “anemia of prematurity” (Schulman 1959). Iron therapy is considered useful; however, such therapy does not effectively prevent the condition (Reedy et al. 1952; Schulman et al. 1954). The two most important conditioning factors are the low absolute iron concentrations at birth, and the accelerated rate of growth characteristic of premature and low birth weight infants (Mackay 1931).

It was previously stated that full-term and preterm infants have circulating hemoglobin concentrations which are proportional to body weight at birth. Therefore, smaller infants have a lower absolute iron content. A problematic variable which is superimposed on the suboptimal iron supply is that the low birthweight or premature infant experiences a period of very rapid “catch-up growth” (Schulman 1959). In the time it takes normal (full-term) infants to double their weight, premature
infants may increase their weight four to six times (Mackay 1931).

Complicating the above situation is the body's slow erythropoietic response to the anemia of prematurity (Schulman et al. 1954). Erythropoiesis is controlled, in part, by the body's need to maintain a constant blood level of oxygen (Gairdner et al. 1952). Since erythropoiesis is depressed following birth because of arterial saturation, erythropoietic activity must be stimulated by a hypoxic condition. The normal erythropoietic response is slow in both full-term and pre-term infants (Gairdner et al. 1955). Therefore it is not uncommon to find extremely low hemoglobin values among premature infants who have depleted their iron stores, are growing at an accelerated rate, and exhibit a variable response to iron therapy (Reedy et al. 1952; Schulman 1959; Schulman et al. 1954).

In normal infants, erythropoiesis begins to resume normal activity at two to three months; however, it can be considerably depressed by infectious disease (Gairdner et al. 1952; Mackay 1933). Iron-deficiency anemia in normal birthweight infants does not occur prior to six months at which time the iron stores from birth are depleted (Josephs 1956). The anemia of prematurity and the iron-deficiency anemia of late infancy are essentially the same phenomenon (Fullerton 1937). The age at onset is determined by absolute iron stores at birth, and rate of growth (Schulman 1959).

**DIET**

The dietary absorption of iron is primarily regulated by the organism's physiological controls, which are designed to maintain a conservative equilibrium, and by the biochemical properties of the foodstuff ingested. In humans, iron is absorbed primarily in the duodenum which is the most alkaline portion of the gastrointestinal tract (Davis 1970). Dietary iron must be exposed to the intestines in a soluble state, in reasonable quantities, and for a sufficient length of time in order to meet the nutritional requirements of the organism (Conrad 1970).

Under normal circumstances the body exerts a strict control over iron balance and iron economy through conservation, reutilization, and by rigid control of the processes by which iron losses are replenished (Conrad 1970). It has been demonstrated that infants can absorb approximately 10% of their dietary iron and that the absorption of bioavailable iron in the infant is comparable to that in the adult male (Heinrich 1970). In contrast, iron-deficient infants can absorb two to three times the normal amount of iron as a means of compensating for iron loss and depletion (Andelman and Sered 1966; Schultz and Smith 1958).

Studies concerned with the bioavailability of dietary iron have demonstrated that the iron content of food varies tremendously (Martinez-Torres and Layrisse 1974; Wretlind 1970). Even among similar food products the iron content may vary depending on where the food is grown and how it is prepared (Bressani 1958; Cook and Monsen 1976). Heme iron is more readily absorbed than ferrous iron, and ferrous iron is better absorbed than ferric iron (Callendar et al. 1957; Hallberg and Sovell 1967; Turnbull et al. 1967). Meat products contribute more iron in an absorbable form and generally enhance iron absorption from vegetable foodstuffs (Layrisse et al. 1968; Layrisse et al. 1969; Martinez-Torres and Layrisse 1971).

Bioavailability of iron is also influenced by dietary constituents such as chelating agents, which can either promote or inhibit iron absorption (Davis 1970; Hwang and Brown 1965; Kuhn et al. 1968). For example, ascorbic acid is a chelating agent that promotes iron absorption by producing a water-soluble iron complex (Moore et al. 1940). Several sugars and amino acids in the diet also decrease precipitation and polymerization and thus enhance the bioavailability of dietary iron (Charley et al. 1963; Martinez-Torres and Layrisse 1970; Pollack et al. 1964). Other compounds such as phytates, phosphates, carbonates, and oxalates strongly inhibit the absorption of dietary iron by effectively binding it into insoluble macromolecules (Conrad 1970; Foy et al. 1959; Hegsted et al. 1949; Hussain and Patwardhan 1959; Sharpe et al. 1950).

In iron-deficiency anemia among infants and children, qualitatively good and bad dietary regimens have been reported in
association with the condition (Davidson et al. 1935; Dawson and Desforges 1958; Josephs 1956; Woodruff 1958). In general, clinical investigations have demonstrated a consistent association between anemia and artificial or prolonged milk feeding (Fullerton 1937; Mackay 1931). Epidemiological studies have also noted that prolonged milk feeding and weaning diets of maize or corn gruels are quite frequently found in association with a high frequency of anemia in infants (Ashworth 1973; Granthan-McGregor et al. 1974; Jelliffe and Blackman 1962). These observations can be attributed, in part, to the relatively high phosphorous content which inhibits the absorption of dietary iron from milk and corn (Lanzkowsky and McKenzie 1959; Martinez-Torres and Layrisse 1974).

The absorption of dietary iron in infants can be impaired by episodes of acute and chronic diarrhea (Conrad 1970). Diarrhea promotes malabsorption by increasing intestinal motility and thereby reducing the amount of time that dietary iron is exposed to the absorptive surfaces of the intestines. In addition, episodes of diarrhea are accompanied by dehydration, loss of appetite, and substitution of solids by starchy gruels which are of lower nutritional quality (Gordon 1963; Scrimshaw 1964).

INFECTION DISEASE

The synergistic relationship between infectious disease and iron-deficiency anemia has a profound influence on the severity of the nutritional disorder and its subsequent relationship to morbidity and mortality in infants and children. It has been noted that most of the severe nutritional disorders rarely occur from the lack of a single nutrient (Scrimshaw and Young 1976). Most nutritional deficiencies are either precipitated by, or aggravated by infectious disease in individuals with borderline nutrient supplies.

Among infants and children from six months to approximately two to three years of age, constitutional and dietary factors precondition the infant to a relatively unstable iron metabolism (Josephs 1953). Infants in this age group also experience a high frequency of respiratory and gastrointestinal infections which can contribute greatly to morbidity and mortality (Gordon et al. 1967). It is important therefore to examine the role of infectious disease in relation to iron economy and the "anemia of infection" (Cartwright et al. 1946) which, in many respects, is similar to iron-deficiency anemia.

Iron is the primary microbial nutrient required by bacterial and viral pathogens to survive and multiply in mammalian host tissue (Weinberg 1966). Many pathogens possess the ability to synthesize siderophores which enable the microbe to compete with the host for iron to meet the growth demands of the microbe (Weinberg 1974). Several experimental studies have demonstrated that iron enhances the growth and virulence of bacterial pathogens (Bullen et al. 1968; Brubaker et al. 1965). Also, it has been noted that iron-binding proteins, such as transferrin and lactoferrin, have a bacteriostatic effect on microbial growth (Bullen et al. 1970; Fletcher 1971; Hanson and Winberg 1972; Martin et al. 1963).

One of the more consistent observations among clinical researchers is that infectious episodes are accompanied by a dramatic reduction in serum iron (Cartwright et al. 1946; Greenberg et al. 1947; Kuhns et al. 1950). This physiological response has been termed "nutritional immunity" and is characterized by the host's ability to induce a hypoferric state which deprives pathogens of essential iron (Brendstrup 1950; Weinberg 1974).

Kuhn and co-workers (1950) have noted that serum iron is quickly removed from the plasma by transferrins which bind iron and store it in the reticuloendothelial system, i.e., liver, spleen, bone marrow. Therefore, iron which would normally be mobilized for hemoglobin synthesis is sequestered from both host and pathogen for the duration of the infectious episode. In adults, mild infections of short duration usually have no significant effect on hemoglobin levels (Cartwright et al. 1946). However, if the infection persists, a normochromic normocytic, or slightly microcytic anemia can develop. In effect, heme synthesis is blocked and hemopoiesis is markedly inhibited (Cartwright et al. 1946).

Among infants and children it has been observed that both
mild and severe infections can result in markedly lowered hemoglobin levels (Davidson and Fullerton 1938; Manchandra et al. 1969). It has also been demonstrated that the return to normal erythropoiesis following an infectious episode was often retarded for several weeks to several months (Fullerton 1937). As a result, infectious diseases occurring prior to iron depletion and during a period of rapid growth can dramatically affect hemoglobin levels, iron economy, and the general nutritional state by interfering with the bioavailability of iron for hemoglobin synthesis (Josephs 1956; Smith 1954; Sturgeon 1956).

Clinical and experimental studies have also demonstrated that children with iron-deficiency anemia are also more prone to develop respiratory and gastrointestinal infections (Andelman and Sered 1966; Beresford 1971; Chandra 1973). This is especially true when iron-deficiency anemia is found in association with protein-calorie malnutrition (Chandra 1973; Masawe 1973). The complications of each particular syndrome serve to lower host resistance and further inhibit the bioavailability of dietary iron for tissue stores and hemoglobin synthesis.

In addition to constitutional factors, diet, and microbial infection, clinical and epidemiological studies have identified a number of important cultural, environmental, and host-specific biological variables that play a role in the etiology of iron-deficiency anemia in infants and children. For example, Gordon and co-workers (1963) have shown that culturally prescribed weaning practices, featuring age- and sex-specific food restrictions and taboos, can contribute significantly to patterns of chronic malnutrition. Likewise, an important environmental variable is parasitic hookworm infestation which may lead to intestinal blood loss and chronic iron-deficiency anemia in tropical and subtropical regions of the world (Bradfield et al. 1968; Roche and Perez-Gimenez 1959; Venkatachalam 1968). Finally, clinical investigations have shown that tissue iron depletion and achlorhydria may contribute to malabsorption of dietary resources by interfering with the normal digestive processes of the gastrointestinal tract (Guha et al. 1968; Hawksley et al. 1934; Smith 1972).

With respect to the problem of morbidity and mortality, it should be noted that infants generally tolerate uncomplicated iron-deficiency anemia rather well. The anemia itself appears to operate as a homeostatic mechanism which functions to balance iron metabolism. Such a physiological mechanism has a strong selective value for a rapidly growing organism that must constantly balance iron economy for nutritional needs and bioavailability on one hand, and host “nutritional immunity” against infectious disease on the other.

It is our opinion that porotic hyperostosis is a consequence of iron-deficiency anemia, and that periosteal reactions are a response to infectious disease. These two phenomena may therefore exhibit a close relationship in a single population. In order to test this hypothesis an age-specific iron stress model has been employed to evaluate the fit of the age-specific distribution of porotic hyperostosis with that of the known age-specific distribution of iron-deficiency anemia among infants and children. Similarly, the age-specific distribution of periosteal reactions will be compared with the known age-specific distribution of infectious disease as it occurs in infants and children. In summary, we propose that the etiology of porotic hyperostosis in infants and children can best be understood in terms of the synergistic interactions among constitutional factors, diet, and infectious disease.

MATERIALS AND METHODS

The skeletal population examined in this study is from the Libben site, a Late Woodland ossuary and habitation site located on the Portage River in Ottawa County, Ohio. The site was excavated during 1967 and 1968 and yielded a sample of 1,327 articulated skeletons of which 452 were classified as infants or children.

The Libben skeletal material is of particular value for a number of important reasons related to sampling procedures. The excavation was characterized by a conscious effort to obtain individuals in all age classes. Fine mesh screening was used to recover term and preterm infants. The age range of the population spanned from approximately 16 weeks in utero to 70 years.
The skeletal materials were in a good state of preservation and there was no evidence of infanticide, or of differential preservation of age classes. Therefore the population is characterized by a minimal amount of sampling bias (Lovejoy et al. 1977).

Radiocarbon dates place the site between A.D. 800-1100, and archaeological analyses suggest a perennial occupation spanning approximately 250 to 300 years (Harrison n.d.). The floral and faunal analysis indicate a diet rich in animal protein, but with little evidence of vegetable foodstuffs.

An analysis of dietary items (Harrison n.d.) indicates that vertebrate remains are represented by 25 identifiable species of mammals (31.6%), 28 species of birds (1.4%), and 10 species of fish (67%). Molluscs and White-tailed deer are rare, and there is little evidence of corn agriculture (Harrison n.d.).

The Libben subadults were aged primarily by dental maturity and secondarily by long bone length and metaphyseal breadth. All dentitions were seriated according to crown and root development. Target ages of one month intervals were established for the first year of life, and thereafter, age intervals of one year were established on the basis of published trends. Specimens without dentitions were aged from polynomial regressions based on long bone lengths, metaphyseal breadths, and cranial base metrics.

Of the 450 subadults (less than 10 years of age) from the Libben site, an operational sample of 241 (53.6%) were scored for porotic hyperostosis and periosteal reactions. A slightly higher number of individuals (N = 11) could be scored for periosteal reactions only. As a result, the number of individuals observed for periosteal reactions amounted to a total of 252 (56%). The criteria for inclusion were based on osteological completeness (i.e., cranial and postcranial material that could be scored for pathological lesions), and reliable age estimates.

In order to avoid a sex bias caused by iron stress among adolescent females (Saddi and Schapira 1970), only infants and children from birth to 10 years of age were included in the study sample. Five age classes were defined based on the known age-specific distribution of iron-deficiency anemia and infectious disease in infants and children (Gordon 1963; Fullerton 1937; Josephs 1936; and Smith 1954). These age classes are: from birth to 6 months; 6 to 12 months; 1 to 3 years; 3 to 5 years; and 5 to 10 years. These age classes were then employed to test the fit of the age-specific distribution of porotic hyperostosis and periosteal reactions at Libben.

All cranial materials were macroscopically examined for porotic hyperostosis while both cranial and postcranial remains were observed for periosteal reactions. The endocranial surfaces of well articulated crania were examined with the aid of a sigmoidoscope lamp.

Those lesions scored as present were then classified as remodeled or unremodeled on the basis of the quality and extent of resorptive bone activity. This procedure was used to more accurately evaluate the age-specific frequency distribution of the two classes of skeletal lesions. It has been demonstrated that bone remodeling rates for infants and children are quite high (Frost 1973); therefore, this aspect of bone behavior is advantageous to the paleopathologist concerned with age-related epidemiological patterns. The criteria for remodeled and unremodeled lesions are as follows:

Porotic Hyperostosis

1. Remodeled Lesions—typically display a smooth lamellar texture with bone filling of the peripheral pores. The microporosity so characteristic of the unremodeled lesion is always absent in the cribriform mesh of the remodeled lesion (Fig. 6).

2. Unremodeled Lesions—usually exhibit sharp and clearly defined margins in the cribriform structure of the hyperostotic bone. The cribriform mesh characteristically displays a microporosity visible upon close macroscopic examination (Fig. 7).

Periosteal Reactions

1. Remodeled Lesions—generally display considerable resorption and redistribution of the new subperiosteal bone as it becomes incorporated into the normal cortex or table of the affected bone. The remodeled bone is usually very smooth, dense, and more mature in appearance than in the unremodeled specimens. Occasionally, the more involved cases exhibit trace hypervascularity and loss of normal bone contour (Fig. 8).
2. Unremodeled Lesions—characteristically display a fibrous, vascular, porous, and somewhat irregular new layer of bone which gives the appearance of a “scab” over the normal cortex or table of the bone (Fig. 9).

Figure 6. Burial 0022a, 5-6 year old child with porotic hyperostosis. A close-up of the left orbit displays remodeling of the lesion with trace hypervascularity and bone filling of the pores.

Figure 7. Burial 01232, 2-3 year old with porotic hyperostosis. A close-up of the left orbit manifests and unremodeled lesion affecting the anterior portion of the orbit, and a remodeled lesion affecting the mid-portion of the supraorbital plate.

Figure 8. Burial 01245, Close-up of an endocranial parietal fragment belonging to a 1-2 year old infant displaying a fairly well remodeled periosteal reaction. Note the smooth, mature appearance and trace hypervascularity.

Figure 9. Burial 05015, Close-up of the endocranial surface of a frontal bone belonging to an 11-12 month old specimen exhibiting an unremodeled periosteal reaction. Note the fibrous, porous, irregular “scab” appearance over the endocranial table.
The remodeled lesions were used to indicate stress episodes which occurred in an individual at an earlier period in life and produced bone response that subsequently healed, or was in the process of healing. Unremodeled lesions were employed to indicate an active disease process which was occurring in an individual at the time of death.

Due to the nonspecificity of the porotic hyperostotic and periostitic skeletal lesions, it was necessary to operationalize a differential diagnosis in our effort to focus upon the iron-deficiency anemia and infectious disease hypotheses as causative agents in the etiology of the two disease processes. Therefore, all skeletal materials were examined for the presence or absence of skeletal alterations which are considered pathognomonic for the more important disease states in which porotic hyperostosis and periostal reactions are commonly found (see Tables 1 and 2).

Four modes of data treatment were employed to evaluate the epidemiological parameters of the nonspecific skeletal lesions, and to measure population fitness. First, a series of histograms, polygon frequencies, and chi square tests were employed to visually display and statistically document patterns in the frequency distribution of porotic hyperostosis and periostal reactions. Yule's Q coefficients were then used to investigate the age-specific measures of association between the two classes of skeletal lesions. Second, the velocity of long bone growth was analyzed in order to evaluate the role of malnutrition and infectious disease in those age classes in which growth retardation was most significant. Third, survivorship curves were constructed for the total population, and for the infant and child subsamples in order to examine patterns of subadult mortality from a populational and subpopulational perspective. Finally, data from clinical, experimental, and epidemiological research were surveyed in order to evaluate the frequency and distribution of the two skeletal lesions in terms of biological and pathophysiologic parameters.

RESULTS

Porotic Hyperostosis

The majority of porotic hyperostotic lesions observed among the Libben skeletal population were of slight to moderate involvement with only a few of the specimens exhibiting excessive tissue hypertrophy. All of the orbital lesions were symmetrical in expression with little variation in the side of involvement. In general, extraorbital lesions such as those affecting the frontal, parietal, or occipital bones were less frequent than orbital lesions. Where extraorbital lesions did occur they were always found in association with the orbital lesions.

It was found that extraorbital lesions occurred with the greatest frequency in the 6 to 12 month age class (Fig. 10). In addition, it is interesting to note that all the subadult specimens aged 6 to 12 months that have both the orbital and extraorbital porotic hyperostotic lesions also have some form of systemic or localized periostal reaction. Beyond the age of 24 months the frequency of extraorbital lesions declines dramatically (Tables 3a and 3b). The quality of expression of extraorbital lesions was consistently slight to moderate with only a few specimens exhibiting extreme reactions. The only endocranial bone changes that have been observed in association with porotic hyperostosis are related to thinning of the endocranial table; however, no such bone changes were seen among the Libben infants and children.

The age-specific distribution of unremodeled porotic hyperostosis indicates that these lesions do not occur before the age of 6 months (Fig. 11a; Table 4a). From the age of 6 to 12 months the lesion exhibits a low frequency. In the 1 to 3 year age class, however, the frequency of unremodeled lesions rises dramatically. Beyond the ages of 3 to 5 and 5 to 10 years, the frequency of unremodeled lesions declines to a relatively low level and appears to remain stable throughout the remainder of childhood (Table 4b). The chi square tests indicate that these age-specific patterns related to age at onset, peak frequency, and age at decline in frequency are statistically significant at the .01 level (Table 4c).
Figure 10. Histogram of the age-specific frequency distribution of both orbital and extraorbital porotic hyperostotic lesions as they occur in association with each other.

Table 3a. The frequency of occurrence of Extraorbital Porotic Hyperostosis.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Present (%)</th>
<th>Absent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-12 mo.</td>
<td>60.0</td>
<td>40.0</td>
</tr>
<tr>
<td>1-2 yr.</td>
<td>41.7</td>
<td>58.3</td>
</tr>
<tr>
<td>2-3 yr.</td>
<td>33.3</td>
<td>66.7</td>
</tr>
<tr>
<td>3-5 yr.</td>
<td>20.0</td>
<td>80.0</td>
</tr>
<tr>
<td>5-10 yr.</td>
<td>10.7</td>
<td>89.3</td>
</tr>
<tr>
<td>Total</td>
<td>29.8</td>
<td>70.2</td>
</tr>
</tbody>
</table>

Table 3b. The frequency of Remodeled and Unremodeled Extraorbital Porotic Hyperostosis.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Remodeled (%)</th>
<th>Unremodeled (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 yr.</td>
<td>30.0</td>
<td>70.0</td>
</tr>
<tr>
<td>2-3 yr.</td>
<td>33.3</td>
<td>66.7</td>
</tr>
<tr>
<td>3-5 yr.</td>
<td>100.0</td>
<td>0.0</td>
</tr>
<tr>
<td>5-10 yr.</td>
<td>33.3</td>
<td>66.7</td>
</tr>
<tr>
<td>Total</td>
<td>40.0</td>
<td>60.0</td>
</tr>
</tbody>
</table>

Table 4a. The frequency of occurrence of Porotic Hyperostosis.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Present (%)</th>
<th>Absent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mo.</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>6-12 mo.</td>
<td>26.3</td>
<td>73.7</td>
</tr>
<tr>
<td>1-3 yr.</td>
<td>51.8</td>
<td>48.2</td>
</tr>
<tr>
<td>3-5 yr.</td>
<td>57.7</td>
<td>42.3</td>
</tr>
<tr>
<td>5-10 yr.</td>
<td>57.6</td>
<td>42.4</td>
</tr>
<tr>
<td>Total</td>
<td>44.4</td>
<td>55.6</td>
</tr>
</tbody>
</table>

Table 4b. The frequency of Remodeled and Unremodeled Porotic Hyperostosis.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Remodeled (%)</th>
<th>Unremodeled (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 yr.</td>
<td>11.8</td>
<td>88.2</td>
</tr>
<tr>
<td>3-5 yr.</td>
<td>46.7</td>
<td>53.3</td>
</tr>
<tr>
<td>5-10 yr.</td>
<td>54.8</td>
<td>45.2</td>
</tr>
<tr>
<td>Total</td>
<td>30.0</td>
<td>69.1</td>
</tr>
</tbody>
</table>
Table 4c. Chi-Square values for the age-specific distribution of Porotic Hyperostosis.

<table>
<thead>
<tr>
<th>Age</th>
<th>0-6 mo.</th>
<th>6-12 mo.</th>
<th>1-3 yr.</th>
<th>3-5 yr.</th>
<th>5-10 yr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mo.</td>
<td>12.86**</td>
<td>49.38**</td>
<td>14.64**</td>
<td>13.35**</td>
<td></td>
</tr>
<tr>
<td>6-12 mo.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>1-3 yr.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>1-5 yr.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
</tbody>
</table>

** Statistical Significance At .01
*** Statistical Significance At .001

Table 4d. Qualitative Assessment of the Degree of Hypertrophic Involvement

<table>
<thead>
<tr>
<th>Age</th>
<th>Slight N</th>
<th>Moderate N</th>
<th>Severe N</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-12 mo.</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1-3 yrs.</td>
<td>43</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>3-5 yrs.</td>
<td>15</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5-10 yrs.</td>
<td>29</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>96</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

A potential problem area in the study of porotic hyperostosis lesions is differential diagnosis. Studies concerned with the biodynamics of erythroid marrow hyperplasia demonstrate that bone marrow proliferation is dependent on the amount of iron available to the marrow (Hillman 1970). In iron-deficiency anemia the level of erythroid hyperplasia is usually self-limiting and generally approximates one to one and one-half times the normal rate (Finch 1970). Occasionally, bone marrow proliferation may reach levels four to six times normal in severe chronic iron-deficiency anemia (Giblett et al. 1950; Hillman and Henderson 1969). Individuals with hemolytic anemia however, often exhibit a marrow response of 5 to 10 times normal with excessive osseous tissue hypertrophy (Finch 1970; Moseley 1974).

The exaggerated response observed in association with hemolytic anemia is due to the increased amount of bioavailable iron which has been retrieved from lysed red blood cells (Smith 1972).

Porotic hyperostosis lesions in the infants and children from Libben manifest only slight to moderate osseous tissue hypertrophy. This observation suggests that the Libben infants experienced a limited level of marrow hyperplasia in contrast to the excessive amount usually experienced in chronic iron-deficiency anemia. Furthermore, the pathognomonic bone changes which are so characteristic of the hemolytic anemias (Moseley 1974) such as sickle-cell anemia (i.e., hand-foot syndrome, vertebral step deformity, ischemic necrosis, and osteomyelitis), and thalassemia major (erythroid marrow hyperplasia of the facial bones, and the rib-within-rib pattern) have not been observed in the infants and children from Libben.

Concerning the problem of differential diagnosis, we can suggest that 1) low levels of tissue hypertrophy in association with porotic hyperostosis, and 2) the absence of skeletal changes which are diagnostic of the hemolytic anemias, are consistent with the hypothesis that porotic hyperostosis in the skeletal material from Libben is the result of iron-deficiency anemia.

Periosteal Reactions

The age-specific distribution of periosteal reactions has rarely been used to investigate patterns of infant and child morbidity and mortality. As a result, a frequency distribution of the specific bones affected by the lesion is presented to aid in the description and differential diagnosis of the reactions (Fig. 12).

Periosteal reactions of the cranium occur frequently on the endocranial table and much less frequently on the ectocranial table, or in the orbits. The orbital lesions have often been mistaken as an expression of porotic hyperostosis (Henschen 1961). However, it should be noted that the pericranial and dural membranes lining the ecto- and endocranial tables are these layers counterpart of the periosteal membrane. Both of these layers of connective tissue have similar vascular and osteogenic properties (Jaffe 1972).

In the postcrania skeletal, it appears that the tibia, humerus, and femur are the most frequently affected by the reaction (Table 5), and that the lesion is often expressed bilaterally. Furthermore, it has been noted that cranial and postcrania lesions
MENSFORTH, et al. / Porotic Hyperostosis / Periosteal Reactions

Table 5. Anatomical distribution of Periosteal Reactions.

<table>
<thead>
<tr>
<th>Location Of Lesion</th>
<th>Distribution Of Periosteal Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Cranium (N=86)</td>
<td></td>
</tr>
<tr>
<td>Endocranial</td>
<td>55</td>
</tr>
<tr>
<td>Exocranial</td>
<td>13</td>
</tr>
<tr>
<td>Orbital</td>
<td>9</td>
</tr>
<tr>
<td>Mandibular</td>
<td>0</td>
</tr>
<tr>
<td>Postcranial (N=86)</td>
<td></td>
</tr>
<tr>
<td>Humerus</td>
<td>28</td>
</tr>
<tr>
<td>Ulna</td>
<td>6</td>
</tr>
<tr>
<td>Radius</td>
<td>4</td>
</tr>
<tr>
<td>Femur</td>
<td>13</td>
</tr>
<tr>
<td>Tibia</td>
<td>45</td>
</tr>
<tr>
<td>Fibula</td>
<td>10</td>
</tr>
<tr>
<td>Ribs</td>
<td>5</td>
</tr>
<tr>
<td>Scapula</td>
<td>5</td>
</tr>
<tr>
<td>Clavicle</td>
<td>3</td>
</tr>
</tbody>
</table>

n = 86 of the most complete cranial and postcranial specimens.

occur more frequently together (40.7%) than individually. These patterns suggest that the pathogenesis of periosteal reactions may be closely related to a systemic disease process. The trend of cranial and postcranial expression of the lesion in the same individual is not statistically significant. Therefore it would appear that the sampling of either cranial or postcranial material alone would not offer an accurate index to the total frequency of the lesion in a population.

The analysis of the age-specific distribution of periosteal reactions at Libben demonstrates that the highest frequency of unremodeled lesions occurs in the first year of life (Fig. 11b; Table 6a). It is in this age class that infant mortality reaches its highest frequency. From the age of one to three years the frequency of unremodeled lesions drops steadily (Table 6b). Beyond the age of three years the lesion displays a consistently low frequency of occurrence. The chi square tests indicate that
these age-specific patterns which relate to age at onset, peak frequency, and age at decline in frequency are statistically significant at the .01 level (Table 6c).

Since periosteal reactions are common in a number of disease conditions (see Table 2), a differential diagnosis was included to objectively evaluate the patterns observed. The criteria for differential diagnosis include the specific bones affected, the location of the lesion on the bone (i.e., metaphysis, epiphysis, dia-

Table 6a. The frequency of occurrence of Periosteal Reactions.

<table>
<thead>
<tr>
<th>Age (mo.)</th>
<th>N</th>
<th>Present</th>
<th>X</th>
<th>Absent</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6</td>
<td>52</td>
<td>26</td>
<td>50.0</td>
<td>26</td>
<td>50.0</td>
</tr>
<tr>
<td>6-12</td>
<td>38</td>
<td>25</td>
<td>65.8</td>
<td>13</td>
<td>34.2</td>
</tr>
<tr>
<td>1-3 yr.</td>
<td>67</td>
<td>35</td>
<td>52.2</td>
<td>32</td>
<td>47.8</td>
</tr>
<tr>
<td>3-5 yr.</td>
<td>26</td>
<td>13</td>
<td>50.0</td>
<td>13</td>
<td>50.0</td>
</tr>
<tr>
<td>5-10 yr.</td>
<td>69</td>
<td>21</td>
<td>30.4</td>
<td>48</td>
<td>69.6</td>
</tr>
<tr>
<td>Total</td>
<td>222</td>
<td>120</td>
<td>47.6</td>
<td>132</td>
<td>52.4</td>
</tr>
</tbody>
</table>

Table 6b. The frequency of Remodeled and Unremodeled Periosteal Reactions.

<table>
<thead>
<tr>
<th>Age (mo.)</th>
<th>N</th>
<th>Remodeled</th>
<th>X</th>
<th>Unremodeled</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-12</td>
<td>23</td>
<td>2</td>
<td>8.0</td>
<td>23</td>
<td>92.0</td>
</tr>
<tr>
<td>1-3 yr.</td>
<td>35</td>
<td>18</td>
<td>51.4</td>
<td>17</td>
<td>48.6</td>
</tr>
<tr>
<td>3-5 yr.</td>
<td>13</td>
<td>5</td>
<td>38.5</td>
<td>8</td>
<td>61.5</td>
</tr>
<tr>
<td>5-10 yr.</td>
<td>21</td>
<td>4</td>
<td>19.0</td>
<td>17</td>
<td>81.0</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>45</td>
<td>47.9</td>
<td>49</td>
<td>52.1</td>
</tr>
</tbody>
</table>

Table 6c. Chi-Square values for the age-specific distribution of Periosteal Reactions.

<table>
<thead>
<tr>
<th>Age</th>
<th>0-6 mo.</th>
<th>6-12 mo.</th>
<th>1-3 yr.</th>
<th>3-5 yr.</th>
<th>5-10 yr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6</td>
<td>.98</td>
<td>7.69*</td>
<td>6.85*</td>
<td>28.75**</td>
<td></td>
</tr>
<tr>
<td>6-12</td>
<td>12.71**</td>
<td>10.70**</td>
<td>36.06**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>.39</td>
<td>8.53*</td>
<td>2.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-5</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = Statistical Significance At .001
** = Statistical Significance At .01

periphysis), and the age-specific distribution of the lesion. For example, it is known that infantile cortical hyperostosis usually affects infants under the age of one year and is characterized by extensive subperiosteal bone proliferation (Jaffe 1972). The condition almost always involves the mandible, clavicles, and ribs (Caffey 1946; Smyth et al. 1946). Reactions as such are very infrequent or entirely absent in the Libben infants. In addition, periosteal reactions are commonly observed in congenital syphilis (Caffey 1939) primarily affecting the metaphysis of the growing bone. In the Libben sample, however, the diaphyses are typically affected with very infrequent involvement of the metaphyses and epiphyses. Also, none of the pathognomonic skeletal alterations usually associated with endemic syphilis have been found at Libben.

Since the Libben diet is high in fish, the possibility of hypervitaminosis A must be considered (Aegerter and Kirkpatrick 1975). Clinical research has demonstrated that the highest fre-
hypervitaminosis A occurs between the ages of one and three years (Greenfield 1975); however, at Libben the highest frequency of periosteal reactions occurs between birth and one year of age (probably prior to weaning). Traumatic injuries are also known to generate periosteal reactions. In the sample of infants and children from Libben only three specimens displayed evidence of bony fracture, and as stated earlier the lesions frequently exhibit bilateral expression. It is therefore improbable that accidental injury was an important epidemiological variable in the pathogenesis of periosteal reactions.

Prematurity has also been suggested as a factor in the etiology of periosteal reactions. However, because of several important physiological handicaps at birth, premature infants are subject to intense selective pressures (Levine and Gordon 1942; Korones 1976) resulting in high neonatal mortality. It is therefore improbable that premature infants could account for the high frequency of periosteal reactions observed throughout the first year of life.

Some of the more probable disease states involved in the etiology of periosteal reactions at Libben include rickets, scurvy, and infectious disease. Rickets is commonly seen in children between the ages of six months to three years (Aegerter and Kirkpatrick 1975). The skeletal changes often associated with rickets (e.g. craniotabes, green stick fractures, and skeletal deformity) have not been observed in the Libben material. Likewise, scurvy generally affects infants between the age of 6 to 18 months. In scurvy, skeletal alterations usually occur in those areas of the bone where growth is most rapid, viz., metaphyses (Jaffe 1971). Also, the deficiency usually results in multiple impaction fractures within the metaphysis. Although the age-specific distribution of scurvy approximates the age-specific distribution of periosteal reactions at Libben, few of the skeletal alterations pathognomonic of scurvy have been observed in the Libben material.

It is well known that periosteal reactions commonly result from supplicative periostitis in response to local and/or systemic infections (Jaffe 1972). In addition, comparative population studies have shown a high frequency of pneumonia, septicemia, otitis media, staph infections, and gastroenteritis among infants and young children during the first year of life in p. societies (Gordon et al. 1967; Hardy 1959; Kaplan et al. Meirning et al. 1974; Mortimer 1973; Rowe 1975; Tonkin 1.

At Libben the great preponderance of unremodeled periosteal reactions occurs in the birth of one age class. These observations suggest that these acute infectious diseases play a primary role in the etiology of these bony lesions.

To briefly summarize the age-related patterns observed for both porotic hyperostosis and periosteal reactions, it can be suggested that both lesions display age-regressive (remodeled lesions), and age-regressive (unremodeled lesions) distributions. However each lesion exhibits its own particular age-specificity with respect to age-at-onset, peak frequency, and age at decline in frequency (see Fig. 11c). It should be noted that statistical analyses which employ gross lumping procedures in assigning skeletal age (e.g., grouping all subadults into the birth to 10 year age class) may significantly distort the age-specific distributions of skeletal lesions which are of value in the study of pathogenesis of disease processes.

Figure 11c. Polygon frequency of the age-specific distribution of unremodeled porotic hyperostosis and periosteal reactions.
Association of Porotic Hyperostosis with Periosteal Reactions

It is often difficult for the paleopathologist to examine the role of synergistic interactions among disease processes. Nonetheless, it is important for the evolutionary biologist to become aware of underlying disease processes and how they can interact. Such an awareness can assist in our attempt to understand human variation in different biocultural settings. Clinical and experimental research has demonstrated that prior to overt iron deficiency, infectious disease can significantly alter hemoglobin levels by sequestering iron in the reticuloendothelial system thereby inhibiting heme synthesis regardless of the nutrient supply (Cartwright et al. 1946). Similarly, clinical and experimental studies have shown that individuals experiencing acute episodes of nutritional deficiency, and especially episodes of chronic malnutrition are more susceptible to infectious disease (Scrimshaw 1964).

In order to evaluate the association between porotic hyperostosis and periosteal reactions it is necessary to consider the age-specificity of both remodeled and unremodeled lesions (Table 7a, 7b; Fig. 13).

Yule’s Q coefficients were calculated to measure the age-specific associations between porotic hyperostosis and periosteal reactions. The numerical values for the coefficients (Table 7c) demonstrate a strong positive correlation between porotic hyperostosis and periosteal reactions in the 6 to 12 month, and the 12 to 24 month age classes. A combined measure of association for the 6 to 24 month period reveals a strong positive association of +.63 (Y = 7.88) which is significant at the .01 level of confidence. After the age of two years no age-specific associations were observed.

The age-specific correlation in the 6 to 24 month age class corresponds to the known age at which iron-deficiency anemia reaches its highest frequency among infants and children. The 6 to 24 month age class also correlates well with the age-specific distribution of the pneumonia weanling diarrhea syndrome which has been implicated as the leading cause of infant and child mortality in industrial and pre-industrial societies (Gordon et al. 1963).
Long Bone Growth at Libben

Patterns of long bone growth have been determined for subadults from Libben. Results from the growth study are presented here to illustrate the effects of infectious disease on long bone growth. Physiological length measurements for the six long bones were recorded for each individual in the age classes between birth to 12 years. Chronological age was determined by seriation of crown and root development of all individuals whose dentition was at least 33% complete and comparison of each with published standards (Schour and Massler 1940; see Lovejoy and Harrison n.d.). During analysis of the data it was noted that infants and children from Libben exhibited a distinctive pattern in the relative rate of growth of the diaphysis, and that this pattern contrasted to the growth pattern of modern EuroAmericans (Maresh 1955). For example it was found that the rate of femur elongation, compared to that of the humerus, was significantly lower at Libben than in Maresh’s study of Denver children. For this reason, the six long bone measurements for each individual in a given age class have been summed, and an age class average has been employed as an indicator of the growth rate for that age class.

In order to eliminate the problem of size, all long bone lengths were normalized by the average adult length for that long bone in the population. The growth data is thus in the form of percent of average adult length achieved by a specific age. After pooling the data from all six long bones, the averages were fitted by least squares (in one year age-class intervals from birth to 12 years) to a curve of the form \( Y = a + bx + c \log x \) which has been shown to fit human growth prior to adolescence with considerable precision (Harrison et al. 1976). In order to determine actual rate of growth the derivative of the fitted curve was obtained for one year intervals and the data are presented in Table 8. An identical procedure was carried out for similar data from the Denver growth study (Maresh 1955).

A comparison of growth rates between Denver and Libben subadults suggests a dramatic difference between the two groups for the rate of growth during the first year of life. Libben growth is slowed during this age class such that a Denver child at age two and one-half years continues to grow at almost the same rate as a Libben child of age one and one-half years. This one

<table>
<thead>
<tr>
<th>Age</th>
<th>Percent Average Adult Long Bone Length Achieved</th>
<th>Growth Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denver</td>
<td>Libben</td>
<td>Denver</td>
</tr>
<tr>
<td>.5</td>
<td>25.1</td>
<td>25.4</td>
</tr>
<tr>
<td>1.5</td>
<td>34.5</td>
<td>32.8</td>
</tr>
<tr>
<td>2.5</td>
<td>40.7</td>
<td>38.0</td>
</tr>
<tr>
<td>3.5</td>
<td>45.8</td>
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<tr>
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<td>50.4</td>
<td>47.0</td>
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<td>54.8</td>
<td>51.2</td>
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<td>6.5</td>
<td>58.9</td>
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<td>66.9</td>
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<td>70.7</td>
<td>67.0</td>
</tr>
<tr>
<td>10.5</td>
<td>74.5</td>
<td>70.8</td>
</tr>
<tr>
<td>11.5</td>
<td>78.2</td>
<td>74.6</td>
</tr>
</tbody>
</table>
year "lag" continues throughout much of the remainder of childhood (see Table 8). From this age class on, the Libben growth rate (albeit retarded) recovers and remains similar to the Denver growth rate for the duration of childhood. It should be noted that some "catch-up" growth may be seen in the 8.5 to 11.5 year age period at Libben. The initial deficit incurred by the early retardation of growth at Libben is eventually made up by delay of the adolescent growth spurt (Lovejoy and Harrison n.d.).

While a number of causes for the early retardation of Libben growth may be suggested, we believe that the data are primarily suggestive of delay by massive infection. The parity of growth rate with Denver children after age four indicates that diet is probably not the primary cause of delay. However the very high frequency of periosteal reactions (Fig. 11b) at Libben does provide a probable cause of growth retardation. Levels of infection sufficient to produce the frequency and extent of periosteal reactions seen at Libben certainly imply high plasma levels of the antiinflammatory adrenocorticoids. Their effects on growth are well known and their inhibition of growth in chronic illness documented (Lowery 1973). Among these effects are a promotion of gluconeogenesis from dietary protein, and a reduction in amino acid availability. At Libben it can be seen by reference to Table 8, and Figure 11b that the ages of reduction and re- assumption (i.e., retardation and acceleration) of growth rate correspond almost exactly with the onset of widespread infectious disease in the population. It would appear, therefore, that in Libben direct as well as indirect physical evidence of massive infection can be observed.

Survivorship at Libben
The paleodemographic analysis of the Libben site skeletal material suggests a robust, successful population with low infant and child mortality (Lovejoy et al. 1977). The population had a crude birth rate of .045, a mean family size of 3.8, and a generation length of 26.6 years. Life expectancy at birth was 20 years. The survivorship data for the total population indicates a type II

Figure 14a. Survivorship curve for the total Libben population.

n=1327

Figure 14b. Survivorship curve for the Libben infants and children aged 0-10 years (n=419 specimens out of the 450 excavated provided reliable age data).
curve which is characteristic of preindustrial societies (Fig. 14a).

The survivorship data for the subadults (Fig. 14b) demonstrates
that the highest rate of infant and child mortality occurred dur-
ing the first three years of life. The highest frequency occurred
in the first year of life (41.4%), with two-thirds of the infants
and children dying by the age of three (66.6%). It should be
noted that the highest frequency of periostal reactions also
occurred during the first year of life (Fig. 11a). From three to
10 years of age the Libben subadults had a low rate of mortality.

DISCUSSION

It is apparent from the parameters outlined in this study that
the accurate diagnosis of disease process must consider all rele-
vant age- and sex-specific factors as they relate to physiological,
biological, cultural, and environmental adaptation. Therefore
models of analysis which utilize age and sex criteria commensu-
rate with the physiological variables of the research problem,
and which include qualitative data relevant to the study of both
morbidity and mortality, will better enable the paleopathologist
to investigate the pathogenesis of disease process and interpret
its role in population fitness.

Recent paleoepidemiological studies have concentrated upon
environmental variables in the etiology of porotic hyperostosis
in skeletal populations. These studies demonstrate that higher
frequencies of porotic hyperostosis occur in areas with high
levels of hookworm infestation, and in areas where staple diets
and food preparation techniques predispose populations to the
poor retention and low bioavailability of iron (Carlson et al.
1974; El-Najjar 1976c; Hengen 1971). Important methodological
limitations in these studies, however, have prevented full con-
sideration of the role of constitutional factors in the pathogen-
esis of porotic hyperostosis. The most important of these limi-
tations has been the practice of partitioning populations into
broad age categories, e.g., “subadult,” birth to 10 years; “adult,”
11 years and over; or “subadult,” “adult male,” and “adult
female” (Carlson et al. 1974; El-Najjar 1976c). Because plasma
levels of iron are sensitive to a variety of influences (rate of
growth, physiological blood loss, infection, prematurity, dietary
shifts, etc.), and because these factors are in many ways age-
sensitive, a more refined age distribution of the lesions is re-
quired in order to isolate the primary causes of porotic hyper-
ostosis in a particular population. It must be remembered that
this lesion is symptomatic of a fundamental imbalance in iron
metabolism, and that such an imbalance can be induced by a
wide variety of factors. So many are the determinants of normal
iron metabolism that it is likely that any single proposed cause
of endemic porotic hyperostosis is incomplete. Accurate diag-
nosis requires as complete and detailed age and sex distribution
data as are possible in skeletal analysis.

A second methodological limitation of earlier studies has
been the failure to note and record the physical character of
the lesion at the time of death. The level and duration of bone
reaction and repair can provide essential information as to the
chronic or acute state of a disorder at the time of death. Because
of the often slow nature of the repair process in some bony
lesions, it is theoretically possible for a sample of adult indi-
viduals to display the skeletal effects of a disorder without
necessarily suffering from the disorder itself at the time of death.
Thus it would be possible for the disease process to acutely
affect only children in a population, while a scheme of classi-
ification which did not utilize the qualitative condition of the
lesion at the time of death would imply a broader age distribu-
tion than actually existed. In addition, careful analysis of the
acute or chronic status of a specific lesion provides data on both
morbidity and mortality associated with a disease process.

In the Libben population, survivorship data indicate a rela-
tively healthy Late Woodland population with relatively low
infant and child mortality. The period of highest infant and
child mortality, however, coincides with the highest frequency
of unremodeled porotic hyperostosis and unremodeled periostal
reactions. In addition, the age-specific distributions of these
conditions in the population strongly fit the known age-specific
distribution of hypochromic microcytic iron-deficiency anemia
and infectious disease as they occur in infants and children.

Contemporary studies concerned with the population pa-
Diet does not appear to be a major factor in the etiology of porotic hyperostosis at Libben. The floral and faunal analysis indicate a high-protein diet (primarily fish and mammals) rich in bioavailable iron and low in chelating agents which inhibit the absorption of dietary iron. In addition, the results of the demographic data, growth analysis, and age-specific distribution of unremodeled porotic hyperostosis and periosteal reactions indicate that chronic malnutrition, which might be attributed to poor diet, culturally prescribed weaning practices, or parasite infestation, is characteristically absent at Libben. Furthermore, recent population research has shown that the nutritional status of a population is dependent upon the interaction of physiological, environmental, and dietary factors (Scrimsheaw and Young 1976). It is therefore more probable that the nutritional stress observed among the Libben infants and children in the one to three year age group is a synergistic response to the nutrient depletion and increased demands which accompany rapid growth, microbial infection, and malabsorption due to weaning diarrhea.

In conclusion, the results of our methodological inquiry lead us to suggest that:

1) the partitioning of skeletal populations into broad age categories may distort important age-specific pathophysiological relationships. Therefore, the accurate diagnosis and interpretation of skeletal lesions requires as complete and detailed age and sex assignments as are possible.

2) skeletal lesions such as porotic hyperostosis and periosteal reactions should be classified as to their physical quality (remodeled and unremodeled) to provide an estimate of both morbidity and mortality as they relate to acute and chronic disease processes.

Furthermore, the age-specific distribution of porotic hyperostosis and periosteal reactions, as observed in the Libben infants and children, lead us to suggest that:

1) porotic hyperostosis is a response to nutritional stress and may therefore be a valuable indicator of the nutritional status of infants and children at the population level.

2) periosteal reactions are a fundamental response to, and therefore a valuable indicator of, infectious disease in infants and children.
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