Porotic Hyperostosis in the Eastern Mediterranean

J. LAWRENCE ANGEL, PH.D.

Curator, Division of Physical Anthropology, Smithsonian Institution, Washington, D.C.

Porotic hyperostosis is bone expansion caused by hypertrophy of blood-forming marrow. It usually affects the skull diploë in adults and the long bones, face, skull vault, and sometimes the trunk in children, often with some thinning and porosity in the cortex and even the formation of a double cortex (bone-in-bone) in severe infections.[1–6] Excess formation of red cells in hematogenous marrow can come from sicklemia or thalassemia (especially in the homozygous form), from other hemolytic anemias including unusual blood defects like spherocytosis, and from iron deficiency anemia.[7,8] Presumably hookworm, amebiasis and other dysenteries, endemic malaria, and even high-altitude anoxia can produce enough anemia to expand the bone marrow space in some people, though there is no detailed evidence for this.

Slight thickening and porosity of bone in ancient skeletons may indicate any of several anemias, either singly or in combination; however, extreme thickening of 3 mm to 7 mm extra diploic thickness in the skull, or marked puffiness of tubular bones in a young child or infant found in an Old World cemetery population, with both strongly affected *and* unaffected children dying unusually early, points to thalassemia (or possibly sicklemia) with both homozygotes and heterozygotes. Such observations would be plausible evidence for falciparum malaria killing the unaffected children and anemia killing the hyperostotic ones on the assumption that thalassemia, like sicklemia, is a true, balanced polymorphism which protects against *Plasmodium falciparum*.[9] If in addition to the above details, the maxillae and the greater wings of the sphenoid in affected children are thickened, thalassemia is likely. If there are few adults involved and the affected child skeletons show joint necrosis and "stepped" vertebral end-plates, sicklemia is likely,[8] as heterozygotes are virtually unaffected in this disease. It is not known how much bone change can occur in glucose-6-phosphate dehydrogenase (G6PD) deficiency (favism). Iron deficiency anemia usually centers on the skull diploë even in children.

In all of these anemias there is great variability in the bone response[3,8] depending on the severity of red cell destruction, the individual hyperplasticity of the marrow, and the location of marrow hyperplasia, often in the entire skeleton in young children, and largely or entirely in the skull diploë in adults. Surface porosity of skull bone alone, usually extracranial, is not porotic hyperostosis and often indicates nutritional deficiency, as in mild rickets[10] or even scurvy, but not anemia.

Material and methods

This study of porotic hyperostosis is based on 1,750 adult skeletons and 584 child and infant skeletons all from Greece and Western Turkey. They were observed and measured on nine field trips since 1937,[11,12] supported in part by the Guggenheim and Wenner-Gren Foundations, the American Philosophical Society, the Smithsonian Institution, Jefferson Medical College, Harvard University, and with the assistance of many unnamed persons.

Presented at the symposium on Paleoepidemiology, 46th Annual Meeting of The American Association of Physical Anthropologists, 14 April, 1977, Seattle, Washington.

Correspondence and reprint requests to Dr. J. Lawrence Angel, Curator, Division of Anthropology, Smithsonian Institution, Washington, DC 20560.

Discussion

Welcker[13] was the first to show from a geographical standpoint how widespread porotic hyperostosis is, with its frequently accompanying thickened cribra orbitalia, in the whole belt from West Africa and the Mediterranean to Indonesia and on to Japan[14] and the New World. The incidence is 5% to 10% on the peripheries and 30% to 45% from Central Africa to Indonesia. The geographic fit of porotic hyperostosis with abnormal hemoglobins and with falciparum malaria is good[15] except in the New World.[16] Here, other anemias must have been responsible, as they must be elsewhere when frequencies of porotic hyperostosis are too high to reflect only abnormal hemoglobins.

The intent of this paper is to look for the origins of these correlations of porotic hyperostosis. The basic data for this problem appear in the Table.

Chronologically, porotic hyperostosis seems to begin at the transition from the Upper Paleolithic to the Mesolithic periods in Africa and the Mediterranean. This theory is based on one of about 20 of the latest Paleolithic adult skulls from Taforalt in East Morocco,[17] a single skull from Sicily,[18] at least four of eight adults from Mesolithic Lothagam (then a peninsula in Lake Turkana), and two of six adults and one infant from the Mesolithic Franchthi Cave at the southeast corner of the Bay of Argos in Greece in the eighth millennium BC strata.[19]

In Early Neolithic times from the seventh through the fifth millennium BC, porotic hyperostosis has been reported in 43% (71) of 165 adult skulls at Çatal Hüyük at about 900 m altitude on the Konya plain in West-Central Turkey,[20] at Nea Nikomedeia (at that time in the coastal marshes of the Haliakmon delta on the Macedonian plain in Greece), and at Franchthi Cave.[21] Of 40 children at Çatal Hüyük only 2 showed marked porotic hyperostosis and 7 slight hyperostosis, although marked porotic hyperostosis occurred in 17% (4) of 23 children plus infants at Nea Nikomedeia, and 39% (9) showed slight porotic hyperostosis, including one bone-in-bone formation.[22] Perhaps the difference in altitude and temperature is significant as suggested by de Zulueta (written communication, October 15, 1975). This general excess of porotic hyperostosis develops with the unusually warm temperatures of Boreal and Atlantic times and with the development and spread of farming in unforested areas of soft soil near water.[23-25] Middle and Late Neolithic and then Early Bronze Age frequencies drop to 21% and 12% overall, but with 50% (7) of 14 adults and 57% (4) of 7 children at the E. B. Cheliotomylos site at Old Corinth next to marshy water channels. After the cooling trend of the Early Bronze Age and the beginning of lower sea levels, Middle Bronze Age Lerna next to a coastal marshy spring[5] shows that porotic hyperostosis decreased to 15% (11) of 73 adults, with strongly affected children and infants (N = 84) down to 8% (7) and slightly

TABLE
Percentage Frequency of Porotic Hyperostosis in the Eastern Mediterranean

PERIOD	ADULTS Slight	ADULTS + and ++	ADULTS Number	CHILDREN AND INFANTS Slight	CHILDREN AND INFANTS + and ++	CHILDREN AND INFANTS Number
Romantic 1800-1900	36 (72)	1 (2)	200			
Baroque 1400-1800	45 (24)	2 (1)	53	—	—	3
Byzantine 600-1400	10 (9)	2 (2)	87	8 (1)	8 (1)	12
Roman 120-600	24 (24)	1 (1)	100	—	—	3
Hellenistic 300 BC-AD 120	12 (17)	1 (2)	138	22 (2)	—	9
Classic 650-300	5 (7)	1 (2)	151	13 (4)	0	30
Early Iron Age 1150-650	6 (7)	1 (1)	114	16 (8)	0	51
Late Bronze Age 1500-1150	8 (17)	1 (2)	215	10 (8)	1 (1)	81
Middle Bronze Age 2000-1500	11 (19)	1 (2)	169	16 (23)	6 (9)	148
Early Bronze Age 3000-2000	11 (37)	1 (3)	332	7 (12)	5 (8)	163
Neolithic 5000-3000	18 (11)	3 (2)	63	9 (2)	5 (1)	22
Early Neolithic	33 (54)	10 (17)	165	25 (19)	9 (7)	75
Mesolithic 9000-6500	17 (1)	16 (1)	6	33 (1)	—	3

Note: Sexes are combined as there is no sex difference in frequency of porotic hyperostosis. + degree = a doubling of diploic thickness; ++ degree = a thinning of outer table and in children, swelling and distortion of long bones. About one fifth of the slight frequency in children is solely cribra orbitalia. In Mesolithic times and for juveniles from Classic times onward samples are too small to be reliable. About 380 infants were omitted, mostly full term, from a Hellenistic well in the Athenian Agora (Angel[8]) since commingling makes study of their skulls difficult. Their inclusion would change the Hellenistic child + infant frequency of porotic hyperostosis.

affected down to 17% (14)—just half of the Early Neolithic level by 1700 BC. Other sites vary widely depending on their proximity to marshes or water which could support anophelines[22]: at Early Neolithic Khirokitia, porotic hyperostosis is 11% (4) of 36 individuals in rocky central Cyprus; at Late Neolithic Kephala, it is 7% (2) of 32 on a rocky headland of Kea island; and at Early Bronze Age Karataş, it is 12% (36) in 300 adults in a fertile Lycian mountain valley far from the lake—all less than at Corinth and Lerna which are near marshy water.

A decrease in sea level to at least 2 m below today's,[24] dryness, and rapidly improving farming techniques[5,12] leading to an increased population density from about 10 to 30/km^2 during the Early to Late Bronze Age[26] should have continued to reduce breeding places for anophelines. This fits the continuation of the virtually straight-line drop in adult porotic hyperostosis from 21% to 2% over the 4,000 years from Late Neolithic to Classical times. But during the turbulent fourth century BC a slight warming of the already more humid climate and the beginning of a rise in sea level ushered in 500 years of more marshiness and warmer temperatures, coupled with some breakdown of farming practices during the epidemics of the later Roman Empire. Porotic hyperostosis increased tenfold during this time, decreased slightly during the Byzantine recovery, and then doubled—not entirely in step with the new silting of valleys in medieval times[27]—followed by the Little Ice Age, with lower sea levels, to modern times.[24] The post-Classical increases in porotic hyperostosis occurred during the known spread and increase of the malarias.[28]

Malaria is the most widespread infectious disease of mankind[29,30] and is caused by several species of sporozoan parasites (plasmodia) which grow and multiply in human endothelium and red cells, but conduct their sex life in the stomach and connective tissue of female anopheles mosquitoes.[31] Each resulting zygote produces an egg container which releases thousands of sporozoites, some of which reach the salivary glands. These sporozoites are injected into the capillary blood of man or other primates when the mosquito bites to obtain its blood-meal. This sets up a continuous parasite cycle between anopheline mosquitoes and humans, monkeys, or anthropoid apes, the success of which depends first on the mutual adaptation or resistance between the human host and specific parasites; second on the adaptation of the anopheline vector; and third on the ecological conditions limiting the activity of the vector. About 50 species of anopheline mosquitoes may serve as vectors,[32] although de Zulueta et al[33] have shown that the European *Anopheles atroparvus* cannot support *P falciparum*. In the Eastern Mediterranean, *Anopheles superpictus*, which prefers cool moving water, and especially *Anopheles sacharovi,* became the probable carriers of falciparum malaria once the postglacial warmth led them to migrate north to Turkey and Greece from Africa and Asia respectively, presumably accompanied by people.[6]

The ecological point seems too obvious to mention: marshes, puddles, streams, and tree-bole water will support larvae of various species of Anopheles despite specific limitations of temperature, salinity, and stagnation, and today, pollution. Hackett[34] uses the summer isotherm of 15 C as the possible malaria limit because of anophelines over-wintering in warm houses, and Garnham[35] makes similar claims even for vectors of falciparum malaria. But Macdonald[36] gives 19 C as the lower limit for vectors carrying *P falciparum* (15 C for *Plasmodium vivax*), and at Early Neolithic Çatal Hüyük with January temperatures perhaps 5 C warmer than the modern 5 C (July temperatures today are 21 C to 25 C), de Zulueta[37] feels that over-wintering may have been impossible; at best falciparum malaria there would have been seasonal, depending on communications or on the warmth of houses during the winter. Anophelines must constantly feed on man in his houses, shelters, fields (*A superpictus* also feeds on domestic animals), and must get one or more of the *plasmodia* from him. Jones[38] and Livingstone[39] both stress the importance of the introduction of farming in greatly increasing the malarias as well as the farmers' later role in controlling them.

An equally critical aspect of the disease, which currently affects 200 million people and causes 2 million deaths per year, is the adaptation of the host to parasites. Most species of vector tolerate all four malarial *plasmodia* with no loss of energy or viability, with the exceptions noted above; this is not true of the human host. *P falciparum* (subtertian malaria) is much more damaging to man than are *Plasmodium malariae* (quartan), *P vivax* (benign tertian), or the rarer and milder *Plasmodium ovale*. Furthermore, *P falciparum* today has a more continuous and central subtropical distribution from West Africa and the Mediterranean to Indonesia and, more recently, to tropical America by migration from Africa; it differs enough in morphology and physiology for some

parasitologists to label it as a separate subgenus (Laverania).[35] Dunn[16] Baker,[40] Bruce-Chwatt[15] and Mattingly[41] all stress that both human adaptation to *P malariae, P vivax,* and *P ovale* and their easy transmission to monkeys and to anthropoid apes suggest that these plasmodial species evolved together with man and other Anthropoidea, probably in Africa and not before the Eocene splitting off of the New World monkeys, who acquired their malaria parasites only recently after contact with humans in South America. This hypothesis of Garnham[35] and Mattingly[41] makes *P falciparum* a comparatively new mutant, less well adapted and hence much more lethal to its vertebrate host than the other three malaria parasites.

The question then emerges of the origin and spread of this last mutant as related to porotic hyperostosis. To answer this we must know what the physiological reactions to *P falciparum* are and how well we can identify these in prehistoric populations. Further questions arise as to the effects of this mutant on prehistoric and historic cultural development; as each society affected has met this challenge differently, the questions go far beyond this paper.

When malarial plasmodia are injected by anopheline mosquitoes in the sporozoite stage, they quickly leave the human bloodstream and go through several sequences of asexual reproduction in endothelial cells lining blood vessels, in skin macrophages, and in the reticuloendothelial tissue of the liver, spleen, or kidney. During this phase, lymphocytes and other white cells can adapt to the parasite and mitigate the infection. At the same time a permanent reservoir of plasmodia can be established during the destructive anemia-producing phase occurring after a week or ten days, when the ameboid plasmodia enter red cells and live by engulfing cytoplasm into their food vacuoles as was shown in electron micrographs by Rodzinska and Trager in bird malaria.[42] Moulder[42] has demonstrated the simplicity of the plasmodium and how in its food vacuole it directly metabolizes its host cell's glucose and protein, plus methionine and perhaps other amino acids from blood serum, for its own support and rapid growth. The available protein is hemoglobin; the parasite uses only the globin fraction of the hemoglobin molecule and discards the heme fraction as pigment which helps to produce the signet-ring appearance of infected red cells. In extreme parasitism, the pigment colors the urine of people with blackwater fever.

Russell[31] emphasizes that while *P vivax* and *P malariae* respectively attack very young and very old red cells, *P falciparum* can enter all ages of red cells at once and complete its asexual reproductive cycle (schizogony) in 36 to 48 hours. Thus the lymphocytes and other white cells cannot easily make contact with this plasmodium in order to produce adaptive antibodies: *P falciparum* is much more infective and produces more anemia than the others. In this situation logical body defences would interfere with metabolism of glucose, enzymatic splitting of the hemoglobin molecule, or use of globin for protein by the trophozoite stage of the otherwise helpless plasmodium. Moulder[42] points out that in people with hemoglobin S (sicklemia) the genetically determined substitution of valine for glutamic acid in the hemoglobin molecule enormously lessens its solubility. This makes the red cell cytoplasm too viscous to be engulfed by the ameboid process, creating a mechanical trap for the plasmodium by exposing it to white cells and their formation of antibodies. Allison[9] has shown experimentally that sicklemia does protect its carriers against falciparum malaria, and Lehmann, Allison, Neel, Cepellini, and others have demonstrated a direct correlation between sicklemia frequencies of 5% to 30% and the occurrence of falciparum malaria. As sicklemia's beneficial effects in the heterozygote are partly counteracted by severe anemia in most homozygotes, this defect is a balanced polymorphism which cannot protect every individual in a population. Other hemoglobin defects and the thalassemias apparently protect in the same way. Glucose-6-phosphate dehydrogenase (G6PD) deficiency (favism) must owe its frequency in malarious populations to a metabolically different but parallel mechanism.

The evolutionary origin of these hemoglobin mutations is uncertain. G6PD polymorphism, and possibly thalassemia, do occur in primates; they may be old mutations originally selected by other malarias in our dryopithecine ancestors and later in the Pleistocene period.

The malarias, therefore, cause some anemia and extra response of blood-producing bone marrow, as well as enlargement of the spleen, according to the severity of infection. These are most marked in falciparum malaria, but sicklemia, and thalassemia especially, demand hypertrophy of bone marrow. In homozygotes this demand is extreme, causing death in adolescence or in early childhood (thalassemia) under prehistoric living conditions.

Can porotic hyperostosis pinpoint the time of occurrence of the mutation which produced the de-

structive *P falciparum*? The earliest skull I know of with grossly hypertrophied diploë by x-ray is the middle Pleistocene skull from Petralona cave in Chalcidice, Macedonia, with an inferior parietal thickness of about 7 mm and a midline sagittal thickness of 11 mm. K. P. Oakely (oral communication, July, 1954) found slight diploic thickening in individual Neanderthals (cf. the Gibraltar skull) though it is not noticeable in Skhul V or IX from Israel, or Shanidar[43] from Iraq. If the Petralona skull's thickening is from thalassemia, the falciparum mutation goes back before 100,000 BC; but this may be an iron-deficiency type of anemia. It would take about a millennium, over 40 generations, to select a protective frequency of any one of the abnormal hemoglobins in a stable population[44]; a very rapid development in terms of human evolution. If the three currently adapted malarias in Australopithecine times produced the same stresses which the falciparum mutant now causes, they might have selected for abnormal hemoglobins again, and these could have persisted at decreasing frequencies through the Pleistocene period until the new mutant appeared.

Real endemicity probably developed in Mesolithic populations which settled near water in the Eastern Mediterranean to fish; it prevailed in the Neolithic period when increased populations settled near marshes produced by rising sea levels and inhabited by *A sacharovi* were attracted north by postglacial warmth.

Can we tell how much of the prehistoric porotic hyperostosis was from abnormal hemoglobins? In Early Neolithic Greece there are 31 useable children and infants at Nea Nikomedeia (23), Franchthi (6), and Lerna (2). Thirteen percent (4) of these have marked porotic hyperostosis and could be thalassemia homozygotes. Using the Hardy-Weinberg equilbrium ($q^2 = .129$), this indicates a recessive gene frequency of .359 and a heterozygote frequency of .460. Of 116 Middle Bronze Age children and infants from Lerna (84), Asine (5), and Hagios Stephanos (27), 8% (9) show severe porotic hyperostosis. The possible thalassemia gene frequency is .278 and the heterozygotes .402. In both time periods we might expect not more than half of the heterozygotes, or about 20% of the population, to be anemic,[45] and porotic hyperostosis should be 20% or less in adults. But porotic hyperostosis in slight and + degrees affects 16 of 24 Early Neolithic Greek adults, or 67%, but only 12% (20) of 169 Middle Bronze Age adults; hence, more than half of the Early Neolithic adult porotic hyperostosis must come from anemia of other causes. This must be even more true of Çatal Hüyük, which was omitted above because of the uncertain representativeness of its infant sample. I suggest hookworm and dysentery as the most likely causes of other anemias there, noting the ritual beds with aurochs-horns in the shrines.[25]

In the New World, porotic hyperostosis occurs with notable frequency in ancient Peruvians,[46] Mayan,[1] and Native North Americans, particularly in the Southwest. The original migrants who came across the Bering platform about 20,000 BC could not possibly have traveled fast enough to bring any type of malaria with them. Dunn[16] shows that the introduction of falciparum and other malarias by slaves from Africa accounts for its destructive New World history, and Arends,[47] Neel,[48] and others have failed to find thalassemia or sicklemia in any modern New World population lacking contact with slaves. However, Bruce-Chwatt,[15] de Zulueta,[33] and others feel that pre-Columbian sea voyages such as those described by Meggers and Evans[49] from Japan to Ecuador in the third millennium BC may well have brought men carrying *P malariae*. While this might explain some of the New World hyperostosis, it is more likely that severe anemias from hookworm and other iron deficiencies were the cause.[50]

This discussion on the possible relation between anemia-produced hyperostosis in ancient skeletons and falciparum malaria typifies the importance of investigating man-disease-environment-culture interaction during the course of human evolution.

REFERENCES

1. HOOTON EA: *Indians of Pecos.* New Haven, Yale University Press, 1930, p 318.

2. CAFFEY J: The skeletal changes in the chronic hemolytic anemias. *Am J Roentgenol Radium Ther* 37:293–324, 1937.

3. WINTROBE MM: *Clinical Hematology,* ed 4. Philadelphia, Lea & Febiger, 1956.

4. BAKER DH: Roentgen manifestations of Cooley's anemia. *Ann NY Acad Sci* 119:641–661, 1964.

5. ANGEL JL: *The People of Lerna. Analysis of a Prehistoric Aegean Population.* Princeton and Washington, D.C., American School of Classical Studies at Athens and Smithsonian Institution Press, 1971.

6. ANGEL JL: Early Neolithic people of Nea Nikomedeia, in Schwidetzky I (ed): *Die Anfange des Neolithikums vom Orient bis Nordeuropa. Fundamenta,* (pt B), vol 3. Koln, Bohlau Verlag, 1973, pp 103–112.

7. MOSELEY JE: The paleopathologic riddle of "symmetrical osteoporosis." *Am J Roentgenol Radium Ther Nucl Med* 95:135–142, 1965.

8. MOSELEY JE: Skeletal changes in the anemias. *Semin Roentgenol* 9:169–184, 1974.

9. ALLISON AC: Polymorphism and natural selection in human populations. Cold Spring Harbor Symposium on Quantitative Biology 29:137–149, 1964.

10. LETTERER E: Uber den Burstenschadel und seine Bedeutung. *Zentralblatt Allgemeine Pathol und Pathol Anat* 85:244, 1949.

11. ANGEL JL: Porotic hyperostosis or osteoporosis symmetric, in Brothwell D, Sandison AT (eds): *Diseases in Antiquity.* Springfield, Charles C Thomas Publisher, 1967, pp 378–389.

12. ANGEL JL:Paleoecology, paleodemography and health, in Polgar S (ed): *Population, Ecology and Social Evolution.* The Hague, Mouton, 1975, pp 167–190.

13. WELCKER H: Cribra orbitalia. *Archiv für Anthropologie* 17:1–18, 1884.

14. KOGANEI Y: Beiträge zur physischen Anthropologie der Aino, I. Untersuchungen am skelet. Mitt aus der Med Fakult der Kaiserl Japan Univ 2:1–250, 1894.

15. BRUCE-CHWATT LJ: Paleogenesis and paleo-epidemiology of primate malaria. *Bull WHO* 32:363–387, 1965.

16. DUNN FL: On the antiquity of malaria in the western hemisphere. *Hum Biol* 37:385–393, 1965.

17. FEREMBACH D: Le nécropole epipaléolithique de Taforalt (Maroc Oriental). Étude des squelettes humains. Centre Nationale de la Recherche Scientifique, Rabat, 1962.

18. ZAINO EC: Paleontologic thalassemia. *Ann NY Acad Sci* 119:402–412, 1964.

19. ANGEL JL: Human skeletal material from Franchthi Cave, in Jacobsen TA (ed): Excavations at Porto Cheli and vicinity. Preliminary report II, The Franchthi cave, 1967–1968. *Hesperia* 38:343–381, 1969.

20. ANGEL JL: Early Neolithic skeletons from Çatal Hüyük: Demography and pathology. *Anatolian Studies* 21:77–98, 1971.

21. ANGEL JL: Anemias of Antiquity: Eastern Mediterranean, in Cockburn E, Cockburn TA (eds): *Porotic Hyperostosis: An Enquiry,* monograph 32. Paleopathology Association, 1977, pp 1–5.

22. ANGEL JL: Porotic hyperostosis, anemias, malarias and marshes in the prehistoric Eastern Mediterranean. *Science* 153:760–763, 1967.

23. BUTZER KW: *Environment and Archeology. An Ecological Approach to Prehistory,* ed 2. Chicago and New York, Aldine-Atherton, 1971.

24. DENTON GH, PORTER SC: Neoglaciation. *Scientific American* 222:100–110, 1970.

25. MELLAART J: *Çatal Hüyük. A Neolithic Town in Anatolia.* New York, McGraw-Hill, 1967.

26. ANGEL JL: Ecology and population in the Eastern Mediterranean. *World Archeology* 4:88–105, 1972.

27. VITA-FINZI C: *The Mediterranean Valleys. Geological Changes in Historical Times.* Cambridge, Harvard University Press, 1969.

28. JONES WHS: *Malaria, A Neglected Factor in the History of Greece and Rome.* Cambridge, Macmillan and Bowes, 1907.

29. FIENNES R: *Man, Nature and Disease.* New York, Signet, 1965.

30. COCKBURN, TA: *Infectious Diseases. Their Evolution and Eradication.* Springfield, Charles C Thomas Publisher, 1967.

31. RUSSELL PE: *Malaria. Basic Principles Briefly Stated.* Oxford, Blackwell, 1952.

32. MAY J: *Studies in Disease Ecology.* New York, Hafner, 1961.

33. DE ZULUETA J, RAMSDALE CD, COLUZZI M: Receptivity to malaria in Europe. *Bull WHO* 52:109–111, 1975.

34. HACKETT LW: Distribution of malaria, in Boyd MF (ed): *Malariology.* Philadelphia, WB Saunders Co, 1949, pp 722–735.

35. GARNHAM PCC: *Malaria Parasites and Other Haemosporidia.* Oxford, Blackwell, 1966.

36. MACDONALD C: *The Epidemiology and Control of Malaria.* London, Oxford University Press, 1957.

37. DE ZULUETA J: Malaria and Mediterranean history. *Parasitalogia* 15:1–15, 1973.

38. JONES WHS: *Malaria and Greek history,* publication 43. University of Manchester, Manchester, England, 1909.

39. LIVINGSTONE F: Anthropological implications of sickle cell gene distribution in West Africa. *American Anthropology* 60:533–562, 1958.

40. BAKER JR: The evolution of parasitic protozoa, in Taylor A (ed): *Evolution of Parasites.* Third Symposium of British Society of Parasitology. Oxford, Blackwell, 1965, pp 1–27.

41. MATTINGLY PF: Origin and evolution of human malarias: The role of the vector. *Parasitalogia* 15:169–172, 1973.

42. MOULDER JW: *The Biochemistry of Intracellar Parasitism.* Chicago, University of Chicago Press, 1962.

43. STEWART TD: *The Restored Shanidar I Skull.* Smithsonian Report for 1958. Smithsonian Institution, 1959, pp. 473–480.

44. WIESENFELD SL: Sickle-cell trait in human biological and cultural evolution. *Science* 157:1134–1140, 1967.

45. SFIKAKIS P, STAMATOYANNOPOULOS G: Bone changes in thalassemia trait. *Acta Hematol (Basel)* 29:193–201, 1963.

46. HRDLIČKA A: *Anthropological Work in Peru in 1913 with Notes on the Pathology of Ancient Peruvians,* Vol 61, No. 18. Smithsonian Miscellaneous Collection, Washington, D.C., 1914.

47. ARENDS T: Current status of the study of abnormal hemoglobins in Venezuela. *Sangre (Barcelona)* 8:1–14, 1963.

48. NEEL JV: The population genetics of two inherited blood dyscrasias in man. Cold Spring Harbor Symposium on Quantitative Biology 15:141–158, 1951.

49. MEGGERS BJ, EVANS C, ESTRADA E: *Early Formative Period of Coastal Ecuador: The Valdivia and Machalilla Phases,* publication 1. Smithsonian Contribution to Anthropology, Washington, D.C., 1965.

50. EL-NAJJAR MY, ROBERTSON A: Spongy bones in prehistoric America. *Science* 193:141–143, 1976.