thousand to several tens of millions of electron volts for the following observables: polarization produced by elastic scattering, differential cross sections for elastic scattering, and reaction and total cross sections. None of the parameters varies with nuclear species, and only one varies with energy.

Polarized protons were used to test the assumptions that reactions involving strong nuclear forces are invariant under parity and time-reversal operations. These experiments bear not only on fundamental symmetries but also on nuclear structure, because they involve the basic interactions.

References and Notes

1. *Proceedings of the Second United Nations International Conference on the Peaceful Uses of Atomic Energy* (United Nations, Geneva, 1958).
2. L. Rosen, J. G. Beery, A. S. Goldhaber, E. H. Auerbach, *Ann. Phys. N.Y.* **34**, 96 (1965).
3. A lucid nonmathematical description of the polarization process is given by H. H. Barschall [*Amer. J. Phys.* **35**, 119 (1967)].
4. Today there are a number of nuclear physics facilities which utilize polarized ion sources. The first was the Minnesota Linac. More recently Haeberli and his students at Wisconsin found a way to prepare negatively polarized ions suitable for acceleration in a tandem electrostatic accelerator. In France, Thirion's group has been successful in the acceleration of very intense beams of polarized protons in a cyclotron.
5. J. Schwinger, *Phys. Rev.* **69**, 681 (1946).
6. C. L. Critchfield and D. C. Dodder, *ibid.* **76**, 602 (1949).
7. M. Heusinkveld and G. Freier, *ibid.* **85**, 80 (1952).
8. M. J. Scott has shown that one can achieve an absolute measure of polarization, also, by performing three independent double-scattering experiments, using an initially unpolarized proton beam [M. J. Scott and R. E. Segel, *Phys. Rev.* **110**, 1398 (1958)].
9. L. Rosen and J. E. Brolley, Jr., *ibid.* **107**, 4154 (1957).
10. M. G. Mayer and J. H. D. Jensen, *Elementary Theory of Nuclear Shell Structure* (Wiley, New York, 1955).
11. T. D. Lee and C. N. Yang, *Phys. Rev.* **104**, 254 (1956).
12. Experiments at the University of Rochester and the University of California, Berkeley, with protons of much higher energy, had shown small polarizations for a few nuclei, but the trend of those data appeared to indicate that polarization would effectively approach zero below 50 Mev. On the other hand, the groups at the universities of Zurich and Wisconsin had observed small polarizations in the scattering of very-low-energy neutrons from a number of nuclei.
13. H. Feschbach, C. E. Porter, V. F. Weisskopf, *Phys. Rev.* **96**, 448 (1954).
14. R. D. Woods and D. S. Saxon, *ibid.* **95**, 577 (1954).
15. See, for example, F. G. Perey, *ibid.* **131**, 745 (1963).
16. My associates and I are indebted to Dr. George Rogosa at the AEC, who made available to us a large fraction of the stockpile of these isotopes.
17. At energies below ~5 Mev one must supplement the calculation of potential scattering with one which takes account of compound elastic scattering—formation of a compound nucleus which decays through the entrance channel. However, this can be done rigorously on the basis of a theory of Hauser and Feschbach, and without the addition of free parameters.
18. F. P. Agee and L. Rosen, "Calculations of Neutron Cross Sections Using a Local Optical Potential with Average Parameters," *Los Alamos Sci. Lab. Rep. LA-3538-MS* (1966), vols. 1 and 2.
19. The work described here was performed under the auspices of the U.S. Atomic Energy Commission. I acknowledge with appreciation the assistance of Mrs. Kay Harper in the preparation and editing of the manuscript.

Sickle-Cell Trait in Human Biological and Cultural Evolution

Development of agriculture causing increased malaria is bound to gene-pool changes causing malaria reduction.

Stephen L. Wiesenfeld

Medical anthropology has been moving increasingly into central areas of anthropological theory. Alland (*1*) has demonstrated some of the ways in which medical anthropology may serve "as a major link between physical and cultural anthropology, particularly in the areas of biological and cultural evolution." The purpose of this article is to examine the relationship between the sickle-cell trait, malaria, and agriculture in east and west Africa so as to derive hypotheses regarding concomitant human biological and cultural evolution.

Malarial infection, both natural and experimental, and mortality from such infection are consistently lower in individuals having the sickle-cell trait (*2*, *3*). The normal population has reduced fertility rates as compared to the "sickler" population in endemic areas (*4*). Also, the distribution of the sickle-cell trait in tropical Africa parallels that of subtertian malaria (*3*, *5*), so it is reasonable to believe that malaria is the selective agent producing high frequencies of the sickle-cell trait in the area of sub-Saharan Africa stretching from the east coast to Gambia on the west coast. Livingstone (*5*) proposed that malaria in west Africa became hyperendemic when large tracts of tropical rain forest were reclaimed for agriculture, by multiplying the number of breeding places for the *Anopheles gambiae* species complex, which contains major vectors of hyperendemic malaria (*6*).

Two important areas in the interaction of the sickle-cell trait, malaria, and agriculture have not been examined previously. First, not all agricultural systems have the same effect on the development of malaria and of high frequencies of the sickle-cell trait. The data presented here show that agricultural systems do differ in this respect, with one, the Malaysian agricultural system (*7*, *8*), having a greater effect than any other. Second, the effects of changes in the frequency of an adaptive gene on the incidence of the disease selecting for it have not been fully examined. Computer models were developed to determine the nature of the interaction of the sickle-cell trait and malaria, and it was found that increasing frequencies of the sickle-cell trait cause reductions in malaria parasitism by reducing the number of people capable of being infected in a population. Both of these arguments are critical to the hypothesis that the development and differentiation of the Malaysian agricultural system is intimately bound to changes in the gene pools of populations using this agricultural system. The action of high frequencies of the sickle-cell trait is to reduce the environmental limitation of malarial parasitism on these populations, thus allowing more human energy to flow into the development and maintenance of the Malaysian agricultural system. A number of lines of evidence are presented here to support the hypothesis.

The author is a medical student at the University of California San Francisco Medical Center, San Francisco. This article is based on a paper presented before the American Federation for Clinical Research, Carmel, California, in January 1967.

Methods and Materials

Data, for the communities of this survey, on the degree of dependence on agriculture, the type of crop regime, and the manner of crop production were obtained from the "World Ethnographic Survey," a continuing series in *Ethnology*. Each community was scored from 0 to 9 according to the reported degree of its dependence on agriculture (0, dependence 0 to 5 percent; 1, 6 to 15 percent; 2, 16 to 25 percent; 3, 26 to 35 percent; 4, 36 to 45 percent; 5, 46 to 55 percent; 6, 56 to 65 percent; 7, 66 to 75 percent; 8, 76 to 85 percent; and 9, 86 to 100 percent).

Data on the frequency of the sickle-cell trait for various tribes in west and east Africa were used only if the sample size was considered adequate. Otherwise, data were used only if confirming studies had been made, in which case the results were pooled.

The mathematical models relating hyperendemic malaria and the sickle-cell gene frequency were set up on the basis of a Fortran IV program and run on the IBM 1401 computer.

Agriculture and the Sickle-Cell Trait

Data from 60 communities in east and west Africa met our criteria; they are plotted in Fig. 1, according to the percentage of individuals with the sickle-cell trait in the community. Data for tribes with agricultural dependence scores of 3 and below were combined, as were those for tribes with scores of 8 and 9.

The 50th percentile (median), the 25th percentile, and the 75th percentile found for each degree of dependence on agriculture show that a greater dependence on agriculture is associated with a higher frequency of the sickle-cell trait. The 25th and 75th percentiles represent the amount of variation around the median. Tribes are ranked either I, II, III, or IV according to which region of Fig. 1 they occupy. The sample of communities having less than 35-percent dependence on agriculture is too small to be considered significant, but communities falling in this region probably have very low frequencies of the sickle-cell trait. There is a trend toward stabilization of the median from 46- to 65-percent dependence on agriculture, but the widest variations in the trait frequencies are found here. Cultures with greater than 66-percent dependence on agriculture show a marked increase in the frequencies of the sickle-cell trait, with a reduction in the amount of variation around the median.

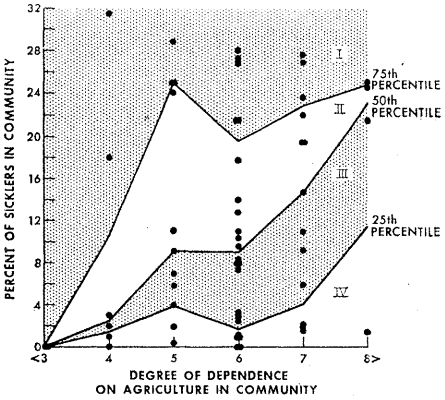

Fig. 1. Relationship between percentage of individuals with sickle-cell trait and degree of dependence on agriculture, in 60 communities.

For any degree of dependence on agriculture there is a wide variation in the frequencies of the sickle-cell trait in various communities, indicating that different relevant variables may differentiate cultures in ranks III and IV from those in ranks I and II. Table 1 shows the distribution of the crop complexes among the four ranks of Fig. 1. Fifty-three of the cultures for which data were available were classified according to their main crop, but this classification does not mean that members of one crop complex may not have crops from another. Cereals, representing crops found in the Sudanic agricultural complex, have a wide distribution but are associated mainly with low frequencies of the sickle-cell trait. Root and tree crops from the Malaysian agricultural complex are associated almost exclusively with higher frequencies of the sickle-cell trait. A more revealing analysis of the relationship between crop regime and frequency of the sickle-cell trait is shown in Table 2. Cereals show wide variation but, for the most part, are associated with low frequencies of the trait. The eight communities in the 25- to 29-percent sickler group do not conform to the normal distribution that would be expected on the basis of data in Table 1. Most of these communities are in east Africa and are societies practicing intensive irrigation of crops. Root and tree crops are clearly associated with very high frequencies of the trait.

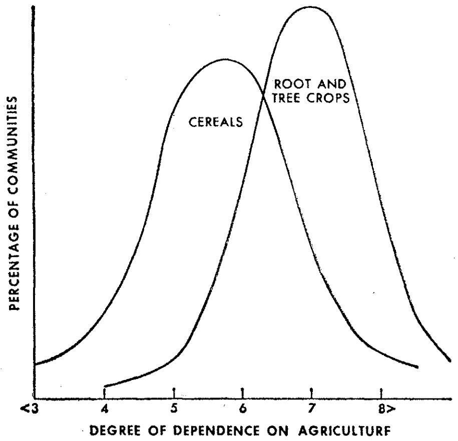

Fig. 2. Normal distribution of the degrees of dependence on agriculture in communities using cereals and in those using root and tree crops.

Also, note that communities with root and tree crops tend to have a greater economic dependence on agriculture than communities using cereals (Fig. 2).

Malaysian Agricultural Complex

According to Murdock (*7*), the predominant root crops in east and west Africa are yams and taro and not the Guinea yam as has been suggested by Livingstone and Chevalier (*9*). The Guinea yam does not have the status of a staple in either of the areas considered. The main tree crops are bananas and coconuts. These root and tree crops all belong to what Murdock calls the Malaysian agricultural complex that was introduced into Madagascar and the coast of east Africa from certain parts of southeast Asia a few centuries before Christ.

The ancient Malayo-Polynesian-speaking Mongoloid peoples of the coastal areas of southeast Asia were excellent sailors who carried their culture eastward into the islands of the Pacific and westward to Madagascar (*10*). The Malagasy are Mongoloid peoples found on Madagascar who speak a language of the Malayo-Polynesian stock which is very closely related to the language of the Ma'anyan of southeast Borneo (*11*). These people once occupied a coastal position and were great navigators. Southeast Borneo lies along the Sabaean Lane, a water route of great antiquity connecting Indonesia, Malaya, the Philippines, southeast China, and India. Dyen (*12*) has applied lexicostatistical methods to Dahl's work and estimates that the separation of the Malagasy from the Ma'anyan occurred at least 1900 years ago.

It is believed that the Ma'anyan brought with them from Borneo swidden agricultural techniques, dry rice, and root and tree crops. The sweet potato also appears to have been introduced at this time. Evidently the wet-rice or paddy-rice cultivation prominent on the mainland of southeast Asia and established on Java and Sumatra around the beginning of the Christian era had not yet been introduced into Borneo. Wet rice appears never to have been adopted by the Ma'anyans, who were, in succeeding centuries of the Christian era, displaced from their original coastal position into the adjacent interior of the island by tribes practicing paddy-rice cultivation (*7*).

The Azanians on the coast of east Africa adopted parts of the Malaysian agricultural complex during the first century of the Christian era, according to early written evidence (*13*). Taro (*Colocasia antiquorum*), yams (*Dioscorea alata, D. bulbifera, D. esculenta*), bananas, and coconuts are still prominent in this area (*14*). These Cushites of Azania carried the agricultural complex west into the interior of Africa and southwest into Uganda (*7*, p. 210).

A solid band of tribes located in what is called the "yam belt" runs across sub-Saharan Africa from the east to the west coast. In all these tribes the Malaysian agricultural complex figures importantly (*7*). Prior to the spread of this complex the Sudanic agricultural complex, with many cereal crops, predominated over native agriculture in sub-Saharan Africa (*7*). Communities practicing agriculture with the Sudanic set of crops were limited to the fringes of the tropical rain forest, because these crops were poorly suited to the rain-forest environment. Also, these communities never attained a high degree of dependence on agriculture in their economies (see Fig. 2). Throughout the "yam belt" there is evidence of the recent development of the Malaysian agricultural complex, which is well suited to the tropical forest environment, and of the recent penetration of the tropical rain forest by Negroid peoples using this complex; this penetration caused the displacement of hunting and gathering pygmy peoples (*15*). It is estimated that the occupation and displacement occurred within the last 2000 years.

Although the crops of the Sudanic complex play only minor roles in the societies under consideration, their planting and harvesting are attended by elaborate ritual, indicating great antiquity. In west Africa the Sudanic complex is more important in the north, where it appears to have arrived at an early date. Also, a number of crops were probably domesticated originally in west Africa, among them the Guinea yams and the oil palm (*16*). However, the Malaysian complex is of great importance in the south, where the tropical forest predominates. Wet rice is cultivated in many parts of west Africa; it appears to have been introduced by Arabs around A.D. 1500 (*17*).

Table 1. The number of communities in each rank, according to crop (see Fig. 1).

Crop	Rank			
	IV	III	II	I
Cereals	15	13	8	7
Root and tree crops	0	1	3	6

Murdock also believes that the Malaysian complex was an important factor in the large expansion of the Bantu peoples through much of tropical Africa, and in the development of forest states in west Africa, due to the suitability of the crops for the tropical forest environment. As noted above, slash-and-burn cultivation is conducive to the development of breeding places for the *Anopheles gambiae* species complex, and thus to the development of intense malaria parasitism. With the shift from use of the tropical forest for hunting and gathering to swidden cultivation, there was a change in the nature of breeding places available to various species of mosquitoes and therefore a shift from *A. funestus* to *A. gambiae* as the major vector of malaria. This shift is significant because the behavior of the species comprising the *A. gambiae* species complex is much more conducive to the development of hyperendemic malaria.

Livingstone (*5*) noted a north-south gradient in the frequencies of the sickle-cell trait, with greater frequencies in the south. All along the "yam belt," especially in the central Sudan and in Nigeria, there is a north-south gradient in the distribution of Malaysian crops (*7*), paralleling the gradient of the sickle-cell trait. Figure 3 shows the distribution of the Malaysian agricultural complex and the distribution of sickle-cell-trait frequencies higher than 5 percent. There is a striking overlap of these areas.

Table 2. Relationship between crop regime and frequency of the sickle-cell trait in 53 communities.

Crop	Percentage of individuals with sickle-cell trait						
	0–4	5–9	10–14	15–19	20–24	25–29	30 and up
Cereals	19	9	5	2	0	8*	0
Root and tree crops	0	0	0	1	6	2	1

* These communities practice extensive irrigation and have high malarial parasitism (see text).

The relationship between agriculture and malaria was noted over a century ago when outbreaks of malaria followed irrigation work (*18*). Angel (*19*) has demonstrated that in the eastern Mediterranean during prehistoric times porotic hyperostosis, or a thickening of the spongy marrow space of the skull due to sicklemia or one of the thalassemias, is associated frequently with early farmers who lived in marshy areas in Greece, but rarely with paleolithic hunters. The frequency of the disease also appears to have decreased in areas where farming methods improved.

Genes and Socioeconomic Adaptations

The introduction of the Malaysian food complexes into sub-Saharan Africa brought about major changes in human ecological niches. Introduction of the crops allowed Negroes to penetrate the tropical rain forest and allowed their populations to increase to new equilibrium levels, making this band across the continent, especially in west Africa, the most densely populated part of Africa. As Geertz (*20*) has demonstrated in Indonesia, a population adopting a new agricultural system which provides a greater and more certain food supply not only undergoes expansion but also tends to involute. More people are centered in one area, and people tend to move less, due to vastly increased needs of husbandry to keep the agricultural system yielding at maximum capacity. Malaria increases in such a situation, for infected individuals remain constantly close to uninfected individuals and the probability of transmission by mosquito increases.

The new agricultural system allows expansion and involution of the population and, at the same time, is the ultimate cause of an increase in malaria parasitism. The population growth puts increased pressure on the agricultural system for greater food production, but the parasitism takes its toll through mortality and morbidity, thus reducing the total energy available for agricultural production. The sickle cell presents a biological solution to a cultural problem by providing many members of the population with genetic immunity, thereby allowing more human energy to flow into agricultural production to meet the demands of an increasing population.

These concepts may be formulated into a principle regarding the interaction of biology and culture in man. Where a socioeconomic adaptation causes a change in the environment, the frequency of a gene will change in proportion to the survival value the gene confers on the carriers in the new ecosystem. Increasing frequencies of an adaptive gene remove environmental limitations and allow further development of the socioeconomic adaptation. The environmental conditions crucial to the transmission of malaria are also crucial to the economy, but the sickle-cell trait removes a limitation for agricultural development and maintenance by reducing the number of people capable of being infected by malaria in a community. The gene frequency and the socioeconomic adaptation continue to develop in a stepwise fashion until either the limit of the gene frequency or the limit of the socioeconomic adaptation is reached.

Evidence to support the hypothesis is found in Table 2 and Fig. 2, which show that societies with the greatest dependence on agriculture have the highest frequencies of the sickle-cell trait.

Mathematical Models: Concepts

It has been possible to develop mathematical simulations relating the dynamics of the sickle-cell trait to the dynamics of hyperendemic malaria. The models show that an increase in the sickle-cell trait reduces the intensity of malaria parasitism by reducing the proportion of the population capable of being infected. The models are offered as evidence that the sickle-cell trait removes an environmental limitation on the development of the Malaysian agricultural complex in Africa. The model presented is believed to be valid for hyperendemic malaria in sub-Saharan Africa. The variables used reflect basic epidemiologic determinants of malarial transmission and are taken from actual field studies. Before considering the models we should consider certain factors of the epidemiology of malaria.

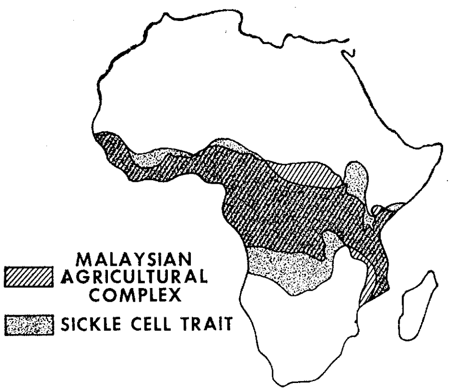

Fig. 3. Distribution of the Malaysian agricultural complex and distribution of sickle-cell-trait frequencies higher than 5 percent.

Malaria is a three-factor disease, with mosquitoes and mammals serving as hosts, and is a disease caused by infection with one of the four malaria parasites; however, only two of them, *Plasmodium falciparum* and *P. ovale*, are important in areas where the sickle-cell trait is found. *Plasmodium falciparum* is usually associated with stable, hyperendemic malaria, while *P. vivax* and *P. ovale* are dominant in areas with unstable, epidemic malaria with marked seasonal variations. Stable malaria, as found in sub-Saharan Africa, is associated with the following characteristics. The mosquito, usually from the *Anopheles gambiae* species complex, bites man frequently, and its probability of survival through the period of development of the parasite in its salivary gland is good. An infective mosquito with a long life span is a greater epidemiologic hazard than a short-lived counterpart. The high longevity of the mosquito in sub-Saharan Africa is due mainly to the humid and stable climatic conditions.

The main vectors for malaria in sub-Saharan Africa are the species of the *Anopheles gambiae* complex and *A. funestus*. The *A. gambiae* species complex is mainly associated with agricultural societies and hyperendemic malaria, while *A. funestus* is associated with areas of unchanged tropical rain forest, hunting and gathering cultures, and lower levels of endemic malaria. This difference in ecological niche is due solely to a difference in the breeding places of the various species, as noted above. The freshwater breeders of the *A. gambiae* species complex will multiply in many types of water but prefer open, sunlit pools of the type created in the tropical rain forest when slash-and-burn agriculture is practiced. *Anopheles funestus* is found in swamps with heavy vegetation, in vegetated river edges, and in other bodies of water that are not in direct sunlight (*21*). Such breeding places are found most readily in the unchanged tropical forest. It is possible to use these mosquitoes as "ecological labels" for different human socioeconomic adaptations, a concept introduced by Audy (*22*).

Figure 4 shows the relationship between the sporozoite rate (or the proportion of mosquitoes, in a population of mosquitoes, with malaria parasites in their salivary glands) and the selective advantage of the sickle-cell trait in seven African communities. The sporozoite rate is a good index of the amount of malaria in an area where it is endemic because the sporozoite rate depends (i) on the number of infected people in a population capable of producing infection in a mosquito, (ii) on the frequency with which a mosquito will bite men, (iii) on the time it takes the malaria parasite to develop within the mosquito, and (iv) on the mortality rate of the mosquitoes (see Appendix, Eq. 3). The selective advantage of the population with the sickle-cell trait is determined according to Livingstone (*23*), and in Africa is represented as some value greater than 1, because 1 is taken as the selective advantage of the population lacking the sickle-cell trait. The greater the selective advantage of the sickler, the more the sicklers will contribute to the composition of future generations. The basic prerequisite for determining the selective advantage of the heterozygote is that the frequency of the sickle-cell gene be in equilibrium with the amount of malaria in the area being considered.

The best-fitting straight line was determined (see Appendix, Eq. 1). The selective advantage of the heterozygote clearly tends to increase as the amount of malaria in an area increases.

Mathematical Models: Results

Figures 5 and 6 are mathematical simulations of various epidemiological conditions and show the dynamics of endemic malaria in response to the presence of the sickle-cell trait in the population.

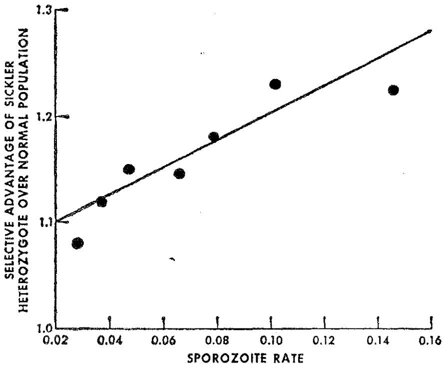

Fig. 4. Relationship between the intensity of endemic malaria (the sporozoite rate) and the selective advantage of the sickler heterozygote over the normal population (see Appendix).

One more epidemiological concept must be introduced before the models are discussed. This is the basic reproduction rate, or the number of human infections produced by an earlier human infection (see Appendix, Eq. 5). If one case of malaria gives rise to two other cases at a later date, then the basic reproduction rate is 2. The basic reproduction rate is directly proportional to the sporozoite rate and serves as a very good index of the intensity of malaria. If the basic reproduction rate ever falls below 1.0, malaria will not continue to be transmitted in the community, so 1.0 represents the critical value for the continuance of malaria. If the basic reproduction rate "continuously exceeds this critical value, malaria will persist but its epidemiological characteristics will be largely determined by the biting habit and longevity of the mosquito" (*24*).

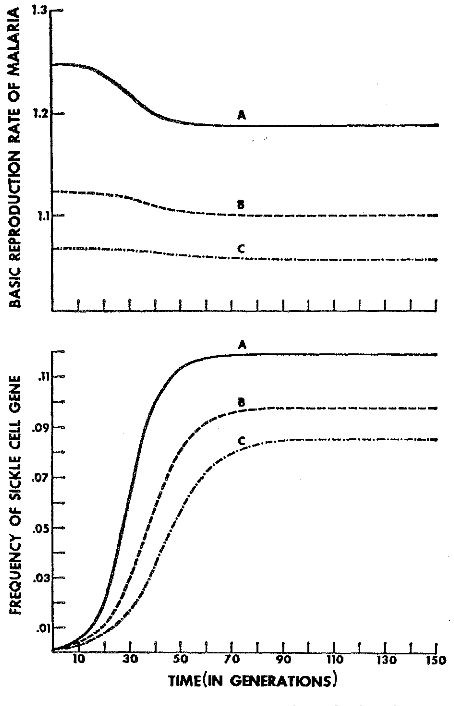

Fig. 5. Mathematical models of the interaction of the sickle-cell trait and malaria in populations where the percentage of human individuals producing the form of parasite capable of infecting mosquitoes is (*A*) 3.6 percent; (*B*) 1.8 percent, or (*C*) 1.0 percent, or where mosquito bites man once every (*A*) 2 days, (*B*) 4 days, or (*C*) 10 days.

The logic of these models may be presented with a minimum of mathematics. The frequency of the sickle-cell gene in a population is assumed to be initially very low, and the longevity of the mosquito and its man-biting habit are taken to be high. For a given sporozoite rate in a particular area it is possible to determine what the selective advantage of the sickler population is, according to the relationship shown in Fig. 4 and in Eq. 1 of the Appendix. For each generation the frequency of the sickle-cell trait is determined for the next generation on the basis of the selective advantage of the sickler (Appendix, Eq. 2). Given this new frequency of the gene, it is possible to see by what degree the population capable of being infected is reduced, hence the value for the basic reproduction rate of malaria for that generation may be determined (Appendix, Eq. 6). Since the basic reproduction rate is directly proportional to the sporozoite rate and the sporozoite rate is directly proportional to the selective advantage of the sickler heterozygote, it is possible to derive an expression relating the selective advantage to the basic reproduction rate (Appendix, Eq. 7), and a new value for the selective advantage is found, which is used in determining the frequency of the gene in the next generation. These three steps —determining (i) the new gene frequency, (ii) the new basic reproduction rate, and (iii) the new selective advantage of the heterozygote—are followed for each generation.

Comparison of the corresponding curves of the top and bottom graphs of Fig. 5 shows that an increase in the frequency of the sickle-cell gene causes a reduction in the basic reproduction rate of hyperendemic malaria by reducing the proportion of people capable of being infected. High sporozoite rates in the mosquitoes, caused by the fact that a relatively high proportion of the human population is capable of infecting mosquitoes, allow development of proportionately high equilibrium frequencies of the gene, which in turn cause marked reductions in the basic reproduction rate (Fig. 5, top, curve *A*). When the proportions of human populations capable of infecting mosquitoes are lower, this allows the development of lower equilibrium frequencies, and this in turn causes lesser reductions in the basic reproduction rate of malaria (Fig. 5, top, curves *B* and *C*). Notice also that it takes more time for lower frequencies to reach equilibrium because of the lower pressures of malaria on the population as a whole.

Figure 5 also shows the effect of varying the mosquito man-biting habit—its effect on the frequencies of the gene developed, and its subsequent effect on the reduction of malaria in a population. The frequencies with which mosquitoes bite man vary a great deal with various species and have profound effects on the nature of malaria in a region. Stable, hyperendemic malaria is associated with high frequencies of biting. Where mosquitoes bite man regularly, the number of infected mosquitoes (the sporozoite rate) is high, the selective advantage of the heterozygote is high, and the frequency of the gene rises rapidly to a high equilibrium value (Fig. 5, bottom, curve *A*). This increase in the gene frequency causes a marked reduction in the basic reproduction rate of malaria. Lower

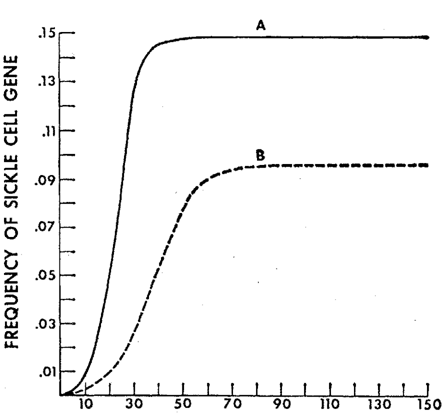

Fig. 6. Mathematical models of the interaction of the sickle-cell trait and malaria where the daily mosquito mortality is (*A*) 5 percent and (*B*) 10 percent.

values for the man-biting habit of mosquitoes allow lower frequencies of the gene to develop, with proportionately milder reductions in the basic reproduction rate (Fig. 5, bottom, curves *B* and *C*).

Increases in the man-biting habit of the mosquito have significant effects on the intensity of malaria and hence on the frequency of the sickle-cell trait. In many parts of the world an increase in the mosquitoes' man-biting habit is caused by the displacement or reduction in numbers of cattle or other animals that previously served as hosts for the mosquito. This displacement is caused by growth in human population, so the mosquito must turn increasingly to man as the major host. Epidemics caused by such a situation have been reported in India (*25*), and it has been speculated that man has caused the displacement of original hosts for many parasites in densely populated parts of the world, especially in the tropics.

Figure 6 shows the effect on the interaction of the sickle-cell trait and malaria of varying the longevity of the mosquito. The daily mortality of mosquitoes depends mainly on humidity and on seasonal climatic variations. Throughout tropical Africa there is relatively little seasonal climatic variation and the relative humidity is constantly high, so the daily mortality of mosquitoes is low. Figure 6, top and bottom, curve *A*, shows a simulation in which a low value was used for mosquito daily mortality, one typical for hyperendemic malaria in Africa, which was determined from actual field studies (*26*). The model stabilized after about 40 generations or 1000 years, and the equilibrium values approximate very closely the values determined for malaria and the sickle-cell trait in Uganda, where values for all the parameters in this model were obtained. MacDonald determined the basic reproduction rate to be around 1.25, and various field studies on frequencies of the sickle-cell trait show values ranging from 27 to 39.1 percent (*27*). For the sickle cell, the gene frequency is half the trait frequency.

On the fringe of the tropical rain forest large areas of savanna are found, where the humidity is lower and where there is more seasonal climatic variation. These conditions cause a reduction in the longevity of the mosquito, the results of which are represented in Fig. 6, top and bottom, curve *B*. The model reaches equilibrium in about 60 generations or 1500 years, and the equilibrium values reached are similar to the values reported for northwestern Nigeria, where the values for the parameters of the model were obtained (*5, 28*). The time necessary for the development of equilibrium in all models is well within 2000 years—the interval since the Malaysian agricultural system was introduced into Africa.

Conclusion

The particular agricultural adaptation we have been considering is the ultimate determinant of the presence of malaria parasites in the intracellular environment of the human red blood cell. This change in the cellular environment is deleterious for normal individuals, but individuals with the sickle-cell gene are capable of changing their red-cell environment so that intense parasitism never develops. Normal individuals suffer higher mortality rates and lower fertility rates in a malarious environment than individuals with the sickle-cell trait do, so the latter contribute proportionately more people to succeeding generations.

In the case of an intensely malarious environment created by a new agricultural situation, the viability of the normal individual is reduced and there is selection for the individual with the sickle-cell trait; this means that the nature of the gene-pool of the population will change through time. This biological change helps to maintain the cultural change causing the new cellular environmental change, and the biological change may allow further development of the cultural adaptation, which in turn increases the selective pressure to maintain the biological change. In this way it is possible to see human biology and culture interacting and differentiating together in a stepwise fashion. If valid, the hypothesis developed here serves to demonstrate the important role that disease may have in human evolution.

Appendix

The mathematical analysis. The purpose of this mathematical analysis is to allow the development of models in which various factors may be varied to determine their effects on the process being considered. The mathematics of the epidemiology of malaria has been developed by MacDonald (*29*), and the basic statements about malaria in this simulation are his. Equations relating to changes in the gene frequency are derived from the Hardy-Weinberg law and the notation of Wright used by Livingstone (*23*).

1) The equation for the relationship between the sporozoite rate and the selective advantage of the sickler over the normal individual shown in Fig. 4 is

$$w_{12} = 1.075 + 1.289s \tag{1}$$

where w_{12} is the selective advantage of the heterozygote sickler and s is the sporozoite rate, or the proportion of mosquitoes capable of transmitting the parasite to man.

2) The expression for the change in gene frequency for one generation is derived from the Hardy-Weinberg law and is given as follows:

$$q_{i+1} = \frac{1}{\left(\frac{w_{11}\,(1 - q_i)}{w_{12i}q_i} \right) + 2} \tag{2}$$

where q is the gene frequency, i is the number of the generation being considered, and w_{11} is the selective advantage of the normal population.

3) The expression for the sporozoite rate is given by MacDonald as

$$s = \frac{p^n ax}{ax - \log_e p} \tag{3}$$

where p is the probability of a mosquito's surviving through the first day of life; p^n is the probability of its surviving through n days, or the time that it takes for the parasite to develop within the mosquito; a is the number of times a mosquito bites a man in one day; and x is the proportion of the human population capable of infecting mosquitoes.

4) To Eq. 3 I have added the following factors: $2q$, the proportion of the human population incapable of being infected due to genetic immunity, and $\alpha = (1-2q)$, or the proportion of the population capable of being infected due to lack of genetic immunity. Rewritten, the sporozoite rate is

$$s = \frac{p^n ax\alpha}{ax\alpha - \log_e p} \tag{4}$$

5) MacDonald defines z_o, or the basic reproduction rate, as

$$z_o = \frac{p^n}{p^n - s} \tag{5}$$

Substituting the value of s from Eq. 4 into Eq. 5, we get

$$z_o = 1 - \frac{ax(1 - 2q)}{\log_e p} \tag{6}$$

6) The selective advantage of the heterozygote may be expressed in terms of the basic reproduction rate through substitution of the expression for s in Eq. 1 into Eq. 5; the substitution yields

$$w_{12t+1} = 1.289p^n[1-(1/z_o)] + 1.075 \tag{7}$$

References and Notes

1. A. Alland, *Amer. Anthropol.* **68**, 40 (1966).
2. A. Allison, *Ann. N.Y. Acad. Sci.* **91**, 710 (1961); A. Motulsky, *Amer. J. Trop. Med. Hyg.* **13**, 147 (1964).
3. A. Allison, *Brit. Med. J.* **1**, 290 (1954).
4. D. Rucknagel and J. Neel, in *Progress in Medical Genetics*, A. G. Steinberg, Ed. (Grune and Stratton, New York, 1956), p. 158; H. Archibald, *Bull. World Health Organ.* **15**, 842 (1956).
5. F. Livingstone, *Amer. Anthropol.* **60**, 533 (1958).
6. What has been called *Anopheles gambiae* is now thought to be a complex of five or more sibling species [G. Davidson, *Riv. Malariol.* **43**, 167 (1964)]. Two of these species (*A. melas* and *A. merus*) are salt-water breeders and three unnamed species are freshwater breeders. The relative role of each species in producing endemic malaria has not been evaluated [P. Russell, L. West, R. Manwell, G. MacDonald, *Practical Malariology* (Univ. of Oxford Press, London, 1963)]. This group of species is referred to in this article as the *A. gambiae* species complex.
7. G. Murdock, *Africa: Its Peoples and Their Culture History* (McGraw-Hill, New York, 1959).
8. The term *Malaysian agricultural complex* is Murdock's. I have adopted Murdock's scheme for the origin and development of this complex.
9. F. Livingstone, *Amer. Anthropol.* **60**, 551 (1958); A. Chevalier, *Rev. Botan. Appl. Agr. Trop.* **26**, 26 (1946).
10. R. Linton, *The Tree of Culture* (Knopf, New York, 1958), p. 45.
11. O. Dahl, *Arhandl. Egede-Inst.* **3**, 1 (1951).
12. I. Dyen, *Language* **29**, 577 (1953).
13. E. Schoff, in *The Periplus of the Erythraean Sea*, E. H. Schoff, Ed. (London, 1912).
14. I. Burkill, *Proc. Linnean Soc. London* **164**, 12 (1953).
15. N. Vavilov, *Chron. Biotan.* **13**, 1 (1949); C. Seligman and B. Z. Seligman, *Pagan Tribes of the Nilotic Sudan* (London, 1932).
16. A. Chevalier, *Rev. Botan. Appl. Agr. Trop.* **32**, 14 (1952).
17. D. Paulme, *Les Gens du Riz* (Paris, 1954).
18. W. Baker, T. Demster, H. Yule, *Records Malariol. Surv. India* **1**, 1 (1929) (reprint of 1847 article).
19. J. L. Angel, *Science* **153**, 760 (1966).
20. C. Greertz, *Agricultural Involution* (Univ. of California Press, Berkeley, 1965).
21. D. Wilson, in *Malariology*, M. F. Boyd, Ed. (Saunders, Philadelphia, 1949), pp. 800-809.
22. J. R. Audy, *Brit. Med. J.* **1**, 960 (1954).
23. F. Livingstone, *Amer. J. Human Genet.* **16**, 435 (1964).
24. G. MacDonald, *The Epidemiology and Control of Malaria* (Oxford Univ. Press, London, 1957), pp. 39-40.
25. S. Christophers, *Sci. Mem. Officers Med. Sanit. Dep. Govt. India* **46**.
26. G. Davidson and C. Draper, *Trans. Roy. Soc. Trop. Med. Hyg.* **47**, 522 (1953); G. Davidson, *ibid.* **49**, 339 (1955).
27. G. MacDonald, *Proc. Roy. Soc. Med.* **48**, 295 (1955); H. Lehmann and A. Raper, *Nature* **164**, 494 (1949); A. Allison, *Trans. Roy. Soc. Trop. Med. Hyg.* **48**, 312 (1954). Gene frequencies represent, almost exclusively, heterozygotes.
28. H. Archibald, *Bull. World Health Organ.* **15**, 695 (1956); A. Allison, *Ann. Human Genet.* **21**, 67 (1956).
29. G. MacDonald, *The Epidemiology and Control of Malaria* (Univ. of Oxford Press, London, 1957).

30. I thank N. L. Petrakis, P. Mustacchi, S. L. Washburn, J. N. Anderson, and F. L. Dunn for aid and helpful criticism. The research reported in this article was supported in part by U.S. Public Health Service fellowship grant 5T5 GM 43-05 and in part by U.S. Public Health Service grant FR-00122 for computing services at San Francisco Medical Center, University of California. The research was also supported in part by PHS research grant CA 05485-07.

Academic Science and the Federal Government

Philip Handler

Responsibility for the welfare of American science with commensurate financial support of research and education in science is a recently established role of the federal government. The rapid growth of this endeavor has occasioned numerous searching inquiries by the executive and legislative branches of the government, by the academic community, and by the press. A growing literature reflects deepening concern with the relationship between science and society, and seeks to develop an appropriate base in philosophy and understanding to guide those responsible for government science policy. This article is intended to provide a more immediate focus for some aspects of this discussion.

Although the Constitutional Convention of 1787 explicitly rejected efforts to grant the federal government constitutional authority for the pursuit of scientific inquiry, over the course of the next sesquicentury that government found itself increasingly involved with science and technology. Nevertheless, before World War II, except for federal support of the state agricultural experiment stations and the highly selective actions of a few philanthropic foundations, research was largely financed from the meager operating funds of those institutions in which it was conducted, that is, universities, a few research institutes, and government laboratories. After the war, augmented support for basic research was provided from funds which, in the American tradition, had been collected or appropriated to further distinctly applied missions, such as a hoped-for cure of cancer or a new weapons system. Private support, particularly of biomedical research, increased greatly, but, by the mid-fifties, the federal government had been established as the major patron of science in our country.

The Office of Naval Research embarked upon an enlightened course of programs for support of research in almost all areas of science. The National Science Foundation was charged with assuring the vitality of American science. As its appropriations increased, the Foundation developed a panoply of individual programs in support of research, science education, and scientific information. Withal, NSF is today responsible for only 15 percent of federal support of research at academic institutions proper. The National Institutes of Health multiplied and, by means of a diversity of programs in support of biomedical research and research training, transformed the nation's medical schools while also strikingly upgrading many departments of biology and chemistry. New agencies, organized to manage exceptionally large enterprises—exploitation of the potential of nuclear energy and the exploration of space—also found it useful to engage the academy in their programs, while the other military services followed the earlier lead of ONR. Occasionally, proponents of a Department of Science appeared, but their proposals were rejected and, instead, there evolved a pluralistic pattern of support not only of specifically mission-oriented research, but of fundamental research at the frontiers as well.

By the historical accident that a pre-

The author is chairman of the department of biochemistry, Duke University Medical Center, Durham, North Carolina.