New Evidence for a Late Introduction of Malaria into the New World [and Comments and Reply]

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Source: *Current Anthropology*, Vol. 16, No. 1 (Mar., 1975), pp. 93-104
Published by: The University of Chicago Press on behalf of Wenner-Gren Foundation for Anthropological Research
Stable URL: http://www.jstor.org/stable/2740950
Accessed: 20-02-2018 22:41 UTC

CURRENT ANTHROPOLOGY Vol. 16, No. 1, March 1975

New Evidence for a Late Introduction of Malaria into the New World[1]

by Corinne Shear Wood

IN A SERIES OF EXPERIMENTS designed to investigate the human physiological factors influencing malaria vectors in their choice of host, new evidence has accrued that gives additional weight to the arguments for a post-Conquest introduction of malaria into the New World. The procedures, results, and implications of the investigations follow a brief introductory account of the dispute.

Malaria has figured prominently in much of human history and today continues as the single greatest destroyer of human populations. The World Health Organization estimated in 1952 that more than 250,000,000 persons, 6.3% of the world's population, were subject to the threat of malaria. Despite more than half a century of organized efforts aimed at eradication, by 1962 there was still an annual toll of 140,000,000 malaria victims (Goma 1966).

While malaria has its most devastating effects within human populations, it is found in the Old World among all major groups of terrestrial vertebrates. Its ubiquity suggests an evolutionary history predating hominids by many millions of years. Coatney et al. (1971) propose a primitive hepatocystis-plasmodium originating in an invertebrate host somewhere in the jungles of Southeast or South Central Asia. They postulate a spread to early tree-dwelling reptiles and, at a much later stage, a proliferation throughout Asia, particularly through the cercopithecoid ancestors of the Old World monkeys. The introduction into Africa is projected as having been accomplished by early apes and man in relatively recent times, perhaps 500,000 to 1,000,000 years ago.

The evolutionary record is necessarily speculative. In contrast, the recorded history of the Old World is replete with descriptions of clinical cases unmistakably referring to malaria victims. Frequent notations of typical intermittent fevers were found in the 800 clay tablets referring to medicine in the library of Ashur Banipal, dating back to 2000 B.C. (Bruce-Chwatt 1965*a*). Hippocrates, in the 5th century B.C., described several forms of malarial fevers. In the same time period in India, Susruta, "the founder of Aryan surgery," recorded clear accounts of malarial fevers, which he attributed to mosquitoes.

Thus, throughout the known history of man in the Old World, malaria's presence has been convincingly documented. However, the consensus found for accounts of malaria in the Old World has not been achieved to date for the New World. There is no controversy regarding the presence in prehistoric times of vectors capable of transmitting malaria, nor is there any question of the devastating effects of malaria among New World populations in recent centuries; rather, the arguments pivot around when the malaria-causing parasites arrived, and with whom.

According to many investigators (Cockburn 1971, Dunn 1965, Johnson 1969, Modell 1968), malaria was unknown in the Western Hemisphere before the arrival of the Europeans and their African slaves. On the other hand, Arcos (in Jaramillo-Arrango 1950), Hoeppli (1959), and Jaramillo-Arrango (1950) insist that malaria existed in the Americas many millennia before the European invasions.

Arcos contends that there is linguistic proof that malaria was rampant in the armies of Pahacutec in A.D. 1378. Jaramillo-Arrango (1950:34) defends this claim, arguing that since it is known that prehistoric Asian populations had malaria, "we see no reason why these primitive discov-

[1] The investigation was made possible by the kind cooperation and direction of Geoffrey Ainsworth Harrison, Department of Anthropology, Oxford University, and Joseph S. Weiner, London School of Hygiene and Tropical Medicine. Eggs and instruction in the care and breeding of the *Anopheles gambiae* were given generously by George Davidson and the staff of the Ross Institute under the direction of L. J. Bruce-Chwatt, London School of Hygiene and Tropical Medicine.

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The present paper, submitted in final form 11 IV 74, was sent for comment to 50 scholars. The responses are printed after the text and are followed by a reply by the author.

erers and colonizers of the New Continent should not have brought malaria with them." The possibility that the first Americans brought malaria with them across the Bering Straits is endorsed by Hoeppli (1959).

The advocates of a pre-Conquest origin of malaria in the Western Hemisphere offer as evidence pictures of mosquitoes on prehistoric pottery from New Mexico and several Mayan words that they translate as "malaise, headaches, chills and fever." Unfortunately, the linguistic evidence derives from manuscripts produced after the Conquest and is likely to contain undue European influence. As an example, Guerra (1964:43) writes, "The books of *Chilam Balam* are copies of copies of codices."

The case for a post-Columbian introduction of malaria has rested upon stronger, albeit inferential, biological, immunological, and historical grounds. In a comprehensive synthesis of the evidence, Dunn (1965) notes that in Africa and Asia plasmodia are found throughout the primate and mammalian world, whereas in the Americas they are found in nature only in man and certain cebid monkeys. In addition, the many genetic red-blood-cell anomalies, such as sickle-cell anemia, Cooley's anemia, G-6-P-D deficiency, and hemoglobin C and E, all found in intimate association with malaria in other parts of the world, were absent in the aboriginal populations of the Americas.

An earlier advocate of a late introduction was Otto Effertz, a physician whose practice spanned parts of Africa and Mexico in the early 1900s. Remarkably ahead of his time, Effertz (1909:260) wrote of the "extreme malignity" of malaria when contracted by natives of America in contrast to "a disease of extreme benignity" for adults in Africa. He argued that in his day much of coastal America was inhabitable only "by pure Africans because on account of malaria, Indians cannot live there. But in the days of the Conquest these areas were the sites of large Indian populations." There is general agreement today that extreme pathogenicity is suggestive of a newly established parasitic relationship (Coatney et al. 1971).

Effertz also recorded that he continually encountered an absolute refusal to take quinine when he attempted to prescribe it for his Indian patients. They insisted that quinine was "too strong for the blood of Indians." Effertz noted that quinine came from a tree of American origin; yet native healers knew nothing of its febrifuge properties. Impressed with the skill and knowledge demonstrated by Indian healers when treating diseases such as syphilis, which he was convinced had a long American history, Effertz remarked that quinine was probably the only American remedy that escaped them. He concluded that his findings suggested strongly that the Indians had not yet accommodated themselves to the new circumstance of recent malaria.

The final arguments against a prehistoric introduction of malaria into the Americas are voiced by several investigators (e.g., Boyd 1941, Bruce-Chwatt 1965*b*, Coatney et al. 1971) who stress that the mechanism of malaria transmission makes it extremely unlikely that malaria could be maintained by small bands of people moving from Asia to the American continent across the cold and arid regions of the Bering Straits. They add that the historical records of the early European conquerors give no indication of their having encountered malaria-like fevers in their many expeditions.

PROCEDURES

The new evidence proposed to strengthen the case for a late introduction of malaria into the Americas is the serendipitous outcome of a series of studies on the influence of several human physiological functions on the choice of human host made by the malaria vector *Anopheles gambiae*. Host selection tests, 151 in all, were made with approximately 3,500 female anophelines and 103 human volunteers, 38 female and 65 male, ranging in age from 15 to 61 years. Each subject agreed to expose each of his or her arms, from fingertip to elbow, to approximately 20 female mosquitoes for two separate tests, each of ten minutes' duration.

The *Anopheles gambiae*, indigenous to the Cameroons, were raised through larvae, pupae, and adulthood in a constant-temperature and humidity-controlled room in which a tropical atmosphere was simulated. The temperature was maintained at 75–88° F., and relative humidity at 70–85%. A 12-hour cycle of day and night was utilized; the night effect was achieved by means of a red 25-watt light bulb suspended from the ceiling (mosquito vision does not extend into the red range) and the day effect through use of a standard flourescent fixture. Because anophelines are nocturnal feeders, all tests were performed during the "night" cycle.

The potential hosts' ABO blood groups were adapted for use as a labelling tag. Blood-group O was represented by 41 of the volunteers, blood-group A by 42, blood-group B by 13, and blood-group AB by 6. Routinely, two subjects who contrasted in ABO status were scheduled for exposure to mosquitoes together. The two volunteers sat next to each other facing the test cage, which contained 20 unfed female anophelines. At a signal from an observer, each volunteer placed an arm inside the cage; the hands were steadied on an inverted paper cup and a gauze sleeve adjusted at the elbow to prevent the escape of any mosquitoes. Two observers stood on the opposite side of the table to record the number and sequence of all observed mosquito landings.

At the conclusion of the first ten-minute run, the arms were withdrawn carefully to avoid the loss of any mosquitoes; the cage was closed and temporarily set aside. The subjects exchanged seats, and another cage of 20 female mosquitoes was placed on the table before them for a second ten-minute trial on their other arms.

The insectary was temporarily brightened when both tests were complete; the mosquitoes were removed from each cage with an aspirator and were introduced into appropriately labelled containers. The mosquitoes were taken to the laboratory, lightly chloroformed, and dissected. The blood meals were removed and placed on glass slides for determination of their ABO status with commercial antisera. All blood-grouping slides were preserved for 24 hours and rechecked.

Strenuous efforts were made to perform the same procedure for each test. All serological tests were unequivocal except for one test early in the investigation in which the blood hemolyzed, possibly because of an excess of chloroform. This test was discarded.

RESULTS

Although various human physiological variables, such as skin pigmentation, age, sex, skin temperature, degrees of subcutaneous fat, and relative nutritional status were compared and evaluated relative to their influence on the mosquito's choice of host, none of these factors could be demonstrated to be acting as host determinants. Nevertheless, it was apparent that choices were made. Under equivalent conditions, some subjects consistently were bitten more; conversely, some were decidedly less attractive to this anopheline. The results of the investigation suggest that a factor which has definite attraction or repulsion value to the mosquito is related, to a statistically significant degree,

to the subject's ABO blood-group status.

The nature of the data suggested several different analyses. A preliminary analysis (table 1) involved the significance of the mean number of blood meals for all tests taken in each blood group. Blood-group O hosted significantly more blood meals when compared with blood-group A and with blood-groups A, B, and AB combined.

TABLE 1
NUMBER OF BLOOD MEALS BY BLOOD GROUP

BLOOD GROUP	NUMBER OF TESTS	NUMBER OF BLOOD MEALS	MEAN	STANDARD DEVIATION
O	140	682	4.87	3.35
A	102	357	3.50	2.89
B	35	153	4.37	—
AB	14	45	3.21	—
A, B, AB combined	151	555	3.67	2.92

Note: Difference between means of groups O and A (2.536) significant at 2% level; difference between means of groups O and all others combined (3.242) significant at 0.2% level.

TABLE 2
MEANS OF LANDINGS AND BLOOD MEALS FOR PAIRED TESTS

	LANDINGS		BLOOD MEALS	
	*Group O vs. Group A**		*Group O vs. Group A**	
Number of tests	101	101	101	101
Mean	5.693	4.693	4.426	3.267
Standard deviation	3.414	2.999	2.733	2.749
	Group O vs. Group B		*Group O vs. Group B**	
Number of tests	28	28	28	28
Mean	6.643	5.429	6.750	4.143
Standard deviation	3.592	2.795	4.535	3.088
	Group O vs. Group AB		*Group O vs. Group AB*	
Number of tests	13	13	13	13
Mean	4.077	4.308	4.154	3.077
Standard deviation	2.100	2.562	2.882	2.216

*Differences significant at .025% level.

To determine more precisely the mosquitoes' preference, means for blood meals and landings for each partner in paired tests (O vs. A, O vs. B, and O vs. AB) were examined for significance within experiment types. Table 2 shows that the mosquitoes clearly preferred to land on and take blood meals from the O subjects in O vs. A tests and to take blood meals from the O subjects in O vs. B tests. Additional statistical analyses of the mosquitoes' choices are presented in a preliminary report (Wood et al. 1972).

DISCUSSION

The findings of this investigation suggest that individuals bearing A or B genes will have a definite selective advantage relative to blood-group O persons in environments where malaria is endemic. This advantage presents a selective force of strength sufficient to counterbalance known pressures of an opposing direction.

An impressive body of evidence implicating the ABO system in the loss of many fetal and postnatal progeny (e.g., Behrman et al. 1960, Bresler 1964, Cohen 1970, Matsunaga and Hiraizumi 1962, Peritz 1971) once led Crow (1960:146) to observe, "It is hard for me to imagine any way in which the ABO polymorphism is sufficiently advantageous to the human species to compensate for its tremendous genetic load."

Many demographic studies indicate that in matings in which the genotype of the mother is OO and that of the father AO, AA, BO, or BB the expected frequencies of the A, B, or O phenotypes are not obtained. Instead, losses ranging from 14 to 32% of the heterozygote genotypes from such matings are observed. Figures vary depending upon the nature of the loss being examined, i.e., sterility, intrauterine abortions, stillbirths, hemolytic disease of the newborn, etc. Unfortunately, studies have focused only on industrialized societies; however, indications are that the losses would be considerably higher under harsh primitive conditions.

Whatever figures are accepted, there is apparently irrefutable evidence of a considerable loss of A and B heterozygotes, a loss of significant biological consequence. Accepting an approximate 25% rate of loss, Levene and Rosenfield (1961:151) find that "such a loss, if not otherwise compensated, would cause an increase in the O gene frequency of the order of .005 per generation."

The findings of this investigation suggest an agent that would mitigate the effects of heterozygote loss due to ABO incompatibility in populations where balanced ABO polymorphisms are found. The vectors of malaria may be acting as an agent of selection, favoring survival and higher reproduction for the A and B genes with a concomitant reduction of the gene for blood-group O.

In a holoendemic environment, i.e., where malaria is a constant threat, the difference in numbers of infected mosquito bites received represents a potential difference in rates of parasitemia. Studies of malaria (e.g., MacDonald 1957) indicate that the level of parasitemia, particularly in the vulnerable child, may be the critical factor determining that child's—and that A, B, or O gene's—chance for survival.

Mourant (1954; Mourant, Kopec, and Domaniewska-Sobczak 1958) records that, by the middle of this century, data on the blood-group status of more than 6,000,000 persons had been published. He notes (1954:10), "Except for South America, ABO frequencies show a marked tendency to small local variation even within the limits of quite small countries." He shows that the ABO distribution is not readily explained as resulting from a drift effect; rather, the pattern suggests that the ABO blood groups are subject to a much more rapid process of natural selection than are the other blood-group systems. For the purposes of the present discussion, the following statement by Mourant (1954:10) is most pertinent: "The most striking example is, however, that of the Indians of South and Central America who even now are almost entirely of group O and may have been exclusively so before the coming of the Europeans."

Serological studies of Asian populations reveal comparatively high values and widespread occurrence of groups A and B. The distribution of the polymorphisms found suggests a long-term adaptation. It is quite improbable that the Asian immigrants to the New World would have failed to possess a portion of these genes. Nevertheless, among the aboriginal populations in the Americas where there has been no European or African contact, blood-group distributions tend to approach 100% frequency of blood-group O.

The unique absence of a balanced ABO polymorphism among the aboriginal populations of the New World sug-

gests that the "buffering mechanism" indicated by this study was not in operation in the New World prior to European and African invasions; hence, unabated negative selection obtained against the genes for A and B. Without malaria, there would be no such selection for the A and B genes as is postulated here. The result would be what is in fact found today in the New World: an overwhelming prevalence of blood-group O.

CONCLUSION

The findings of this investigation provide additional inferential evidence supporting the case for a late introduction of malaria to the American continent. If, as the data have shown, the vectors of malaria choose more hosts with blood-group O, many of the persons possessing this blood type will suffer disadvantage such that the association with malaria will favor blood-groups A and B in that population. Conversely, in the absence of malaria, the naturally occurring selection against groups A and B due to mother-child ABO incompatibility would result in time in the virtual elimination of the A and B genes from the population. The implication of the unique American ABO distribution is that no force selecting for the presence of blood-groups A or B, such as malaria, was present until quite recently. As a result, ABO incompatibility pressures remained unopposed, and A and B genes declined to their present levels.

Abstract

New evidence is offered to strengthen the case for a post-Conquest introduction of malaria into the New World. An investigation of human physiological factors influencing host selection by malaria vectors revealed a strong preference by *Anopheles gambiae* for human hosts with blood-group O. The unique, overwhelming group-O frequency present among indigenous American populations is seen as a result of mother-child ABO incompatibility effects operating in the absence of the positive selection pressures by malaria vectors favoring enhanced survival for genes A and B that the investigation findings suggest. It is proposed that had malaria been present to act upon the original gene pool, a balanced ABO polymorphism would be found in the New World Indians today.

Comments

by J. LAWRENCE ANGEL

Washington, D.C., U.S.A. 2 IX 74

For a long time, scientists have speculated on some heterozygote advantage to explain persistence of the ABO polymorphism. Possible selective factors are antigenic effects of flesh versus vegetable foods, as hinted by Kelso and others, favoring B or A in vegetarian groups; disease; and "hybrid vigor." Wood's disease-carrier data amplify these elegantly.

She does not estimate the selective advantage over O of A, B, and AB phenotypes in a malarial environment, apparently because she cannot know the extent to which Mediterranean, Asiatic, and American anophelines prefer type-O blood, although both northwestern European and American emphases on type O could fit a preference like that of *Anopheles gambiae.* In any case, a quite slight malaria-anopheline selection pressure could balance the incompatibility-caused O increase.

More troubling is the pathogenicity of different malarias. *Plasmodium malariae, vivax,* and *ovale* each cause only intermittent sickness in habituated populations. Only *P. falciparum,* the new mutant, kills the unadapted human host lacking abnormal hemoglobins or other protection for survival of children who have not yet built up antibodies. Wood's selective mechanism favoring A and B in the Old World would work well only where falciparum malaria existed, and we don't yet know when it got into China; severe anemia in East Mediterranean populations from 8000 B.C. onward suggests that falciparum malaria was spreading into Africa and Asia from this or a nearby center (assuming that the anemia is from abnormal hemoglobins). No anemia is obvious in the Upper Cave Choukoutien skulls (still lost, unfortunately), and late Pleistocene climate was probably too cold for anophelines or malaria among the northern Eurasiatic hunters, including ancestors of Paleo-Indians. Wood's hypothesis for the New World works nicely. For the Old World, however, I doubt that there is microevolutionary time for her selective mechanism by itself to account for the current frequencies of A and B blood antigens, since it depends, I think, on the spread of falciparum malaria. Other selective mechanisms must also favor A and B.

by ALICE M. BRUES

Boulder, Colo., U.S.A. 22 VIII 74

This is an interesting matter, though it does not tell the whole story of hemispheric differences in the ABO system. For instance, there is really quite a lot of A in North America; and the selection suggested here would still require some kind of selective disadvantage of homozygous As and Bs as compared to heterozygotes to explain the upper limits of A and B allele frequencies where malaria *has* been a selective factor. Most interesting are the possibilities for similar investigations of other insect vectors of disease. We are left in the dark, in fact, as to whether the American species of *Anopheles* have the same tastes and distastes as *A. gambiae.* The predilections of *Aedes,* the yellow-fever mosquito, would be equally important. Also, we should not be so impressed by the correlation with ABO blood group as to overlook the possibility of specific insect-repellent properties of certain individuals which are not associated with any such obvious marker. For instance, I am so repugnant to fleas that I am unaware of their presence in a room until told by someone who is being bitten; I share this property with some but not all members of my immediate family, so I assume it is a Mendelian trait. It is a laughing matter now, but would not have been when bubonic plague was abroad in the land, with fleas a principal vector. Unfortunately mosquitoes, gnats, horseflies, ticks, and chiggers dine on me with the greatest gusto, indicating that these attractions and repellencies may be quite specific. Insect host preferences have been extensively studied in plants; it is time to study them in humans.

by MARIE STRIEGEL CLABEAUX

Buffalo, N.Y., U.S.A. 29 VII 74

Wood makes a timely contribution with her fresh approach to a long-standing problem in prehistoric epidemiology. The application of serological techniques (and of immunological and related biochemical procedures) to contemporary populations should open new pathways in the study of questions of the evolution and historical distribution of disease. Conclusions based on evidence derived from a single perspective, be it osteology, archeology, primatol-

ogy, linguistics, serology, etc., will be much more limited than those reached through the synthesis of data gathered by multiple methodologies. Wood strengthens her own conclusions by succinctly summarizing much of the previous work in the field.

Recognizing that this is a preliminary study, I should like to express the hope that future work will include the examination of larger samples and a more detailed account of testing procedures with respect to "various human physiological variables, such as skin pigmentation, age, sex, skin temperature, degrees of subcutaneous fat, and relative nutritional status." What was the composition of the test sample in regard to these variables? How were relationships between the variables checked? Were test pairs used for these variables as they were for the ABO blood groups? Perhaps pairing of ABO types within and between geo-ethnic populations would prove of value.

The natural history of disease in the New World contains numerous differences from that of the Old World, due to factors such as ecological variations and differences in the population densities of human groups. Thus the conclusion that malaria was absent in the New World, though more or less ubiquitous in the Old World, is inherently acceptable. Wood has added one more argument to buttress an already good case. At the same time, she suggests an additional factor in the apparent fixation of the O gene. I hope that this synthesizing study portends a new trend in historical bio-anthropology.

by THOMAS E. DURBIN

Turlock, Calif., U.S.A. 22 VIII 74

Wood's findings are well substantiated by the Amerindian ethnohistory of the Central Valley of California and that of the northerly valley systems of Oregon and Washington. The great epidemic of A.D. 1829–33, which swept south from Ft. Vancouver through the interior valleys of the Columbia, Willamette, Sacramento, and San Joaquin rivers to the Los Angeles Basin, has been almost certainly identified as malarial in the excellent studies of Cook (1955*a*, 1962). The fact that the historically recorded distribution of the malady is identical with the modern distribution of the *Anopheles* mosquito on the western coast of North America prompted Cook to his conclusions. The progress of the malady, which decimated the aboriginal population of the area affected, was documented by the few Europeans familiar with region and its peoples at that time (McLoughlin 1941, Townsend 1905, Work 1945). From these works one may conclude that the epidemic was perhaps the single greatest factor in the virtual extinction of the aboriginal population of central California, Oregon, and Washington before A.D. 1850 (Cook 1955*b*:70).

There had not been significant contacts between the Amerindians and Europeans or Asians in the area at that time, as the former population dwelt in the interior and the latter remained along the coast. Only a few Spanish punitive expeditions and some Yankee fur-trapping and exploratory groups had entered the interior, none remaining for more than a few days. The malaria must have been communicated from one Amerindian to another from Ft. Vancouver south along the then entirely aboriginal trade routes of the interior (Cook 1960, 1962). I have noted archaeological evidence of possible epidemic interments in Yokuts cemeteries of that period, with mass graves and many infant burials, in the northern San Joaquin Valley (Durbin 1971, Durbin, Napton, and Pope 1974). It was this area of the San Joaquin Valley through which J. J. Warner journeyed between Sacramento and Los Angeles, recording only eight living Amerindians in 1832 and nothing save skeletons in 1833 (Branch 1881:94; Gilbert 1879:12).

As the known distribution of remnant Amerindian blood types in this area has been noted as demonstrating a typically vast majority of group-O individuals, and in view of the above archaeological and ethnohistorical evidence, it would appear that Wood's conclusions are sound for the western coast of North America.

by MARCUS S. GOLDSTEIN

Jerusalem, Israel. 18 VII 74

This paper is a valuable contribution. It summarizes admirably the arguments pro and con as to whether malaria occurred in the New World before Columbus. The attempt to clarify this problem by means of an imaginative, carefully controlled experiment is most laudable. And the author, with fine restraint, submits her experimental findings as merely suggestive. Indeed, I agree with Wood that the case for a post-Columbian introduction of malaria appears stronger than the contrary. A word about the experiment, an ingenious one: I am not clear how the mosquitoes would "know" which person had which blood group. This question apparently occurred to Wood and her co-workers (Wood et al. 1972), for they note, "The basis for this recognition and selection [of blood-group O in its feeding] is not obvious, although ABH [O?] blood-group substances occur on skin cells and have been reported in sweat." Additional research on this question would seem to be in order. In regard to the given tabular results, the differential in mean landings or blood meals, albeit statistically significant, is actually small; there is, in fact, a greater difference between the means of the Group Os in Group O vs. Group A, Group O vs. Group B, and Group O vs. Group AB (table 2) than between O and respectively A, B, or AB. Were there any individuals who had no "bites"? Relatively how many, in which blood groups? In short, I would agree that the finding "needs . . . to be confirmed and extended to other strains of *An. gambiae* and other Anophelines" (Wood et al. 1972), especially since the statistical results, in my opinion, are inconclusive.

The discussion by Wood of the ABO polymorphism in man in general and in relation to malaria in particular strikes me as provocative with respect to the past and present biology of man; the issues raised seem to me to merit amplification and consideration in depth. The possibility of computer simulation in this regard might be explored (cf. Brues 1963). Whether the apparent tendency of *A. gambiae* to prefer the blood of people with blood-group O occurs among those with the sickle-cell trait would also be of interest (see Wiesenfeld 1967). In sum, I found the paper highly stimulating, and I hope Wood continues with her experimental efforts.

by R. L. HALL

Corvallis, Ore., U.S.A. 27 VIII 74

With its comprehensive presentation of the problem of malaria in the New World, including ethnohistorical, historical, parasitological, and experimental aspects, this paper makes a fine contribution to the developing field of medical anthropology. The weakest link in the chain of inferences, it seems to me, is the inferred connection between relative susceptibility to mosquito bites and susceptibility to malaria. It seems logical to assume that the more bites, the more likely one would contract the disease—provided that infected *Anopheles* behave as uninfected ones do and provided that in areas of endemic malaria even a relatively small

number of bites does not produce sufficient dosage for contraction of malaria.

Altogether, the argument presented in this paper is an interesting and important one, and deserves further consideration and further testing.

by J. MICHAEL HOFFMAN

Berkeley, Calif., U.S.A. 3 IX 74

At first glance this appears to be an interesting picture Wood has presented us—that because *Anopheles gambiae* selectively feeds on individuals of blood-type O versus A, B, or AB, the latter blood types would be positively selected for, and this would counterbalance the loss of A and B genes through maternal-fetal incompatibilities. This would lead to the ABO polymorphisms seen in so many areas of the world today. But since the New World native populations show such an overwhelming proportion of O individuals, Wood argues that the positive selective force for maintaining genes A and B was not present in pre-Columbian times. In the absence of conflicting data, this certainly seems plausible, but there are some problems with her data and arguments.

First, I wonder why *A. gambiae* was used as the test vector. As she points out, this is a species indigenous to the Cameroons, not the New World. I would have thought it much more appropriate to have used *Anopheles* species indigenous to this hemisphere, of which more than a dozen have been linked with malaria transmission (Da Silva 1967, Giglioli 1968). Would *A. darlingi* show the same predilection for type-O blood as *A. gambiae*? Only experimentation could tell. That one species' predilection is the same as another's is too much of an assumption.

Secondly, as several commentators remarked following Otten's (1967) article in this journal, to show an association between two variables is quite different from demonstrating causality. Unfortunately, Wood does not attempt to deal with this question except in a way that brings me to my final criticism.

Wood is ostensibly dealing with the problem of malaria, yet her focus is on mosquitoes, the vector of malaria and not the agent. By arguing that mosquitoes, here *A. gambiae,* bite more O people than others, she implies that the O people would get more malaria. *Non sequitur!* It must be demonstrated that those who get the bites get the malaria. What if the *Plasmodia,* the agents of malaria, had a predilection for blood-types A, B, and AB? What blood groups then would show higher incidences of malaria? Wood's data indicate that the mosquitoes *tend* to prefer type-O blood, but they still feed on individuals with A, B, and AB blood. What this suggests is that perhaps we have here a meaningless association—maybe we should be looking rather at what causes malaria instead of what carries it.

Also, Wood gives a hint at how well her data would stand up when she speaks about "serendipitous outcomes." Such outcomes are indeed the result of most research, but they should first be taken by themselves as the thrust of a new study to support the implications originally seen. This I hope Wood will actively pursue in the near future, for it is an intriguing problem and I believe she has taken an interesting pathway toward its solution.

by FRANK B. LIVINGSTONE

Ann Arbor, Mich., U.S.A. 3 VIII 74

Despite the intriguing experimental results reported in this paper, the major conclusion does not follow from the evidence, or at least there are many tenuous assumptions in between. First, the biting preferences with regard to the ABO blood groups have been found for one species, *Anopheles gambiae,* which is confined to tropical Africa and surrounding islands. It is a long jump from this evidence on one mosquito population to the assumption that all anophelines have the same preferences, especially when it is known that within the *gambiae* species complex there are enormous differences in host preferences, some being almost completely anthropophilic and others highly zoophilic. Second, the frequency of mosquito bites is assumed to be related to the amount of selection by malaria by the connecting assumption that the degree of parasitemia will be correlated with the frequency of bites. A high degree of parasitemia is known to be associated with increased mortality, but an association of the frequency of bites with parasitemia within a population is not very close despite its plausibility. There is still controversy as to the relationship of malaria mortality to malaria endemicity, which is measured by the number of infective bites per unit of time, and it is very possible that epidemic malaria or malaria with low endemicity may actually cause more mortality than highly endemic malaria. Many infectious diseases are known to cause greater mortality in a population where their transmission is interrupted or diminished. Third, the experiments and the author's comments imply that malaria selects against OO homozygotes. However, if in addition to incompatibility selection this is the only selection operating at this locus, it would result in the elimination of the O allele and the fixation of the A and B alleles, and no balanced polymorphism would occur, contrary to the author's statement. There is no consideration of this problem in the article, and no analysis of the population dynamics of the locus is done at all. This is comparable to making assertions about gravitation and not using Newton's Laws. Finally, the world distribution of the ABO blood groups and its implications for the hypothesis are not even mentioned. Many American Indian populations are homozygous for blood-group O, but I am not convinced that all the A and B blood-group occurrences in American Indians can be attributed to post-Columbian admixture. In pre-Columbian times the American Indians were remarkably free of most infectious diseases that ravaged the Old World, such as smallpox, malaria, plague, cholera, and even syphilis, contrary to the source cited in the paper. There is a great likelihood that this absence of disease was related to their homozygosity for blood-group O. Obviously the balancing factor for the ABO blood groups was not present in many American Indian populations, and neither were many of the diseases that have been shown to have an association with the blood groups. In the Old World, infectious disease was undoubtedly a major factor controlling population growth, which would make it a very effective selective factor; in the New World, human sacrifice and warfare seem to have been more important, although the problems of population growth are only now beginning to be explored. How does the idea of malaria as the balancing factor accord with the frequencies of the A and B alleles in the Eskimo, the Ainu, the Australian Aborigines, the Lapps, or the Polynesians, all of whom have surely not been subjected to selection by malaria? Since the hypothesis of this paper raises all these problems, it seems to me of limited value. Selection by malaria has probably had little effect in determining the variation in ABO frequencies among human populations.

by ROBERT D. MCCRACKEN

Denver, Colo., U.S.A. 3 IX 74

Wood deserves to be congratulated on a clever experiment. The results certainly raise many fascinating questions. However, one thing the results do *not* do is to lend much support one way or the other to the debate concerning

the time of introduction of malaria into the New World.

First, there is the problem of sample selection. How and where were the subjects obtained? What was their racial background and medical history, and, perhaps critically, what were their dietary differences? How often did the subjects bathe, and what soaps, colognes, and perfumes did they use? What other items in the environment, including clothing, had their skins come into contact with prior to the experiment which might have accounted for the differences? Lack of information on these things alone makes the data suspect.

In interpreting the data, Wood appears to confuse statistical and biological significance. The former does not necessarily imply the latter. For instance, in terms of mortality or impaired reproductivity, what is the difference between a blood-meal mean of 4.87 for blood-group O and 3.50 and 4.37 for blood-groups A and B respectively (see table 1)? After all, 140 people shot dead with an average of 4.87 bullets are just as dead as a group of 102 people shot dead with an average of 3.50 bullets, even though the differences may be statistically significant. Further, according to data in table 1, differences in blood meals between blood-groups O and B are not significant, nor is there much difference between A and AB. Wood might as well forget about blood-group B in terms of her argument, for clearly blood-group A accounts for most of the variance. In order to make a strong argument, she will have to show that differences are significant in terms of reproduction and not just statistically.

Data in table 2 reveal what happens when a mosquito has a choice between what are presumably two different blood groups. But what has such a choice to do with the real world? The data may in fact prove quite the opposite of Wood's point. They show that even when mosquitoes have a choice they will bite persons of all blood groups, and that when they don't have a choice, which is probably much of the time for any given mosquito, they will take whatever ABO blood group is available. Here, I think, we see an example of the dangers of applying laboratory experiments to the real world.

Wood's article is too short. She doesn't go far enough in her analysis and discussion. It would have been more interesting, and she might have made a better case for herself, if she had presented more detailed ABO blood-group distributional data, showing differences between specific groups who have had long- and short-term exposure to malaria, gradations between such groups, etc.

by JOHN M. MCCULLOUGH

Salt Lake City, Utah, U.S.A. 5 IX 74

Wood has shown the increased susceptibility of O blood-type individuals to *Anopheles gambiae* bites. From this she infers that blood-type O is very common in New World natives because no malarial selection against the O locus operated during pre-Columbian times; as a corollary, blood-types A and B are common in the Old World because of selection vis-à-vis malaria despite heavy fetal wastage of A and B alleles from ABO incompatibility. Research results are impressive, and the basic idea of selective advantage is appealing.

The ABO locus has been closely implicated with other diseases (Robinson, Tolchin, and Halpern 1971, Reed 1962, Buettner-Janusch 1959), and further tests of the ABO-malaria association should be pursued to complete the picture. For instance, Wood's interpretation of selective advantage assumes that the probability of contracting malaria, with consequent selective effect, is a simple function of "blood meal" frequency, regardless of blood type; this may or may not be so. Reanalysis of Firschein's (1961) original data for Belizan Black Caribs in terms of ABO phenotypes and net reproductive performance would be enlightening, given this new idea.

The implications of Wood's hypothesis could be applied to modern population dynamics. For example, Blacks were brought in large numbers to Latin America (Mörner 1967), but their present distribution is very spotty. In Yucatan, an endemic malarial region with moderate mortality (Hilferty and Maher 1933), Black and Black-Indian mixture comprised an estimated 14% of the population in 1742 (Aguirre Beltrán 1946), yet recent blood work shows that only 1 rural Yucatec in 515 (0.2%) has the Hb^S allele (Cabannes et al. 1971), and I^A and I^B are still fairly low (Matson 1970). The Mexican East and West Coastal areas were heavily malarial, yet only 0 to 2% of "Indians" have Hb^S, while 0 to about 10% of coastal "hybrid" populations have the allele, and the A and B genes are comparatively low in both groups (Lisker 1971). If the sicklemia trait is in low frequency despite its supposedly strong protection from malaria, how do the A and B blood types fare? Were genetic isolation (Wolf 1959, Crawford and Workman 1974) and social selection so strong in lowland Mexico as to withstand a very effective biological selection pressure? Perhaps so, but the question merits further investigation (Friedlander 1969). On the other hand, in South America, Blacks have prospered, often to the demographic disadvantage of the Indian (Whitten 1965).

A last consequence of Wood's hypothesis should be the lowered incidence of the I^O allele in Old World areas with a high malarial endemicity. My cursory "eye-balling" of some allele frequency maps does not show this to be the case, but selective interaction of the ABO locus with other malaria-related loci (Hb^S, G-6-PDd, thalassemia) should be taken into account before final judgment is made.

In conclusion, I find Wood's article stimulating in begging more interesting questions and research than it directly answers.

by CHRISTOPHER MEIKLEJOHN

Winnipeg, Canada. 3 IX 74

The evidence presented by Wood appears to be internally consistent. To that degree, I am impressed by it. I would like to add emphasis to the absence of the malarial parasite in nonprimate species in the New World. Without such a reservoir, it is hard to envisage the maintenance of malaria in early New World hunter-gatherer populations, whose group size would be well below that required to sustain an endemic disease pattern.

I wonder, however, whether Wood has provided any real proof for her hypothesis. The figure quoted for the increase in gene frequency of O per generation in the absence of the malarial vector suggests a major selective force. On the face of it, this is very strong circumstantial evidence for the argument. However, other observations make her hypothesis liable to question. I would simply like to mention two:

What forces maintain the rather complex geographic patterning of ABO frequencies in areas of the Old World *not* subject to malaria? In the other polymorphisms that Wood lists as highly correlated with malarial distribution, a pattern of sharp clines is noted. Why is this not so for ABO? The geographical patterning is far more complex. There does not appear to be any clear evidence of higher frequency of O in Old World areas not directly subject to malaria.

If the selection pressure is as high as suggested, then the maintenance of B in Eskimo populations makes it appear

that they are very late New World arrivals. However, all the recent work on Eskimo-Aleut origins seems to suggest an antiquity of at least 10,000 years in the arctic environment (see, e.g., Laughlin 1967).

The above observations are not meant to disprove Wood's hypothesis. They are simply meant to demonstrate that it cannot explain all Old and New World ABO frequencies. I am reminded of the point made by Loomis (1967) in discussing skin colour: Many theories have provided explanations for one end of the spectrum of variation; what is required is one that can explain the total range.

by A. E. MOURANT

London, England. 9 IX 74

Wood has, in a very clear manner, marshalled most of the important evidence for and against the presence of malaria in the New World in pre-Columbian times and shown that its presence is extremely improbable. Her own studies (Wood, Harrison, Doré, and Weiner 1972) add substantially to the evidence. However, as she herself admits, the differences which these workers found between observed and expected frequencies of being bitten are statistically only barely significant. Moreover, data on associations of blood groups with diseases, which fall into the same general category of information, tend to show differences between the results of different observers, the reasons for which are not always understood. Therefore, while fully realising the extreme care which went into the investigation, I suggest that it is of such importance that it should be repeated by an independent team of workers.

Athreya and Coriell (1966), reviewing very fully the evidence which then existed on associations between malaria and blood groups, showed that the geographical distribution of blood-group B in the Old World tends to correspond with a high rate of endemicity of malaria at the present time or in the recent past. They suggest that this is because the possession of the blood-group B antigen confers a selective advantage against malaria. Similar geographic associations are found (as mentioned by Wood et al.) between malaria endemicity and the genes for haemoglobin S, for β-thalassaemia, and for glucose-6-phosphate dehydrogenase deficiency, and are almost certainly to be explained by similar selective advantages. However, in the case of the first and last of these there is additional evidence in the form of parasite counts on individuals of different genotypes. Among the suggestions made by Athreya and Coriell for further research is "correlation of severity of parasitic infection as evidenced by high parasite count, anemia, hemolytic crisis, and blackwater fever with the blood group of the patient."

Rather surprisingly, in view of the vast amount of data which exists for or against associations between blood groups and most of the common diseases, there are very few data indeed relating to malaria. In the course of an exhaustive search of the literature, my colleagues Dr. Ada Kopeć and Mrs. K. Domaniewska-Sobczak and I have found only four relevant papers, those of Minkievich (1925), Lizunova (1925), Rubaschkin, Moldawskaja, and Pauli (1927), and Farr (1960).

Among 1,159 Uzbek malaria patients, Minkievich found a non-significant excess of group A, while among 875 persons from Voroneszh with malaria Lizunova found a non-significant deficiency of A. Rubaschkin et al. found a marked excess of group AB among 636 malaria patients from Kharkov and Mariupol; these authors also quote the work of others, but without references or separate control figures. Farr tested only 112 Bristol blood donors who had previously suffered from malaria and found no significant difference from controls. Taken together, these papers lead to no clear conclusion.

There is, in addition, a considerable number of published papers on blood groups in relation to therapeutic malaria, much used as a treatment for syphilis and other conditions in the days before antibiotics. Here, however, totally different considerations arise, for the blood group of the donor of the infected blood markedly and predictably affects the result.

It may be concluded from the fascinating papers of Wood and of Athreya and Coriell (which should be read together, for one complements the other) that it is important both that the work of Wood et al. (because of its very importance) be repeated by others and that extensive surveys be done of the blood groups of malaria patients. The results would be of importance not only for the history of this most important of all infections, but also in relation to its current pathology.

by WILLIAM S. POLLITZER

Chapel Hill, N.C., U.S.A. 5 VIII 74

Wood is to be congratulated on an intriguing and ingenious hypothesis bearing on both complex questions of ABO blood-group distribution and malaria in the New World. It appears to add one more link to the chain of arguments supporting the absence of malaria in the preconquest Americas. There are, however, some unanswered questions.

Anopheles gambiae is a common vector of the malarial parasite in Africa, but it is a recent import—1930—to the New World. Among the most important vectors in the Americas are members of a different subgenus, such as *A. punctipennis* and *A. quadrimaculatus*. Would comparable experiments with them show the same results?

No mention is made of the species of malaria. *P. falciparum* of malignant tertian malaria is involved in the balanced polymorphism with sickle-cell and perhaps other anemias; *P. vivax* of benign tertian malaria and *P. malariae* of quartan malaria are apparently not. The origin of them in the New World is thought to be different. May not this also influence the hypothesis? Also often overlooked in discussion of disease origins is the likelihood of evolution of parasites themselves over great time periods.

While the reasoning about the likely introduction of groups A and B into the New World is probably correct, it is also possible that they were eliminated in Asia or in the Americas for causes unrelated to malaria, such as other epidemics. Group O would then remain the sole blood factor, with or without malaria.

by FRANCISCO M. SALZANO

Porto Alegre, Brazil. 5 VIII 74

The results presented in this paper are undoubtedly interesting, and it is worth pursuing this line of research to verify if the findings are reproducible using different mosquito densities, other malaria vectors, and persons of different ethnic background; the inferences drawn, however, are debatable. My criticisms of the theory presented are the following:

1. While there is no doubt that the Indians living in the Amazonian region and adjacent Venezuelan and Brazilian territories uniformly show blood-group O, the situation in the Andes is less clear; my impression is that there are too many A, and sometimes also B, individuals to be accounted for by admixture only (Salzano 1957, 1964). In North America, on the other hand, Matson and Schrader (1933) have reported a high prevalence of A in the Blackfeet and related tribes.

2. The generalization of the findings to the New World

situation can be challenged on the basis of at least two facts: First, the subjects in the experiment were presumably Caucasian, and there is no guarantee that the results would be the same in persons of Indian ancestry, since skin color is undoubtedly an important factor in mosquito attraction. Secondly, in the Western Hemisphere some 13 species of *Anopheles* have been linked with malaria transmission, and the main vector is *A. darlingi*, not *A. gambiae* (Giglioli 1968).

3. It is difficult to envisage a mechanism that would link ABO blood-group composition with attractiveness to mosquito bites.

4. There are so many factors involved in the maintenance of the ABO polymorphism (for a synthetic review see Gershowitz and Neel 1970) that it is hard to believe that the simplified picture presented by Wood could be true.

by LOWELL E. SEVER

Los Angeles, Calif., U.S.A. 6 VIII 74

The paper by Wood is an interesting and important contribution to two areas of investigation: the history of malaria and natural selection operating at the ABO locus. My comments are restricted to the second of these areas.

Many of us have wondered for some time about the maintenance of a polymorphic state at the ABO locus, where the recognized selection mechanisms, such as fetal wastage (Chung and Morton 1961) and ABO hemolytic disease (Sever 1969), would operate against the A and B alleles in most populations (Sever 1969). The selective disadvantage of O individuals in a malarial area suggests a mechanism which would operate against the O allele in some populations.

In her discussion of maternal-fetal ABO incompatibility, Wood points out that the studies which have been done have "focused only on industrialized societies; however, indications are that the losses would be considerably higher under harsh primitive conditions." There are some data which would appear to support that suggestion. In a study of fertility in two Japanese mining-town areas, Matsunaga and Itoh (1958) estimated a mortality rate due to maternal-fetal ABO incompatibility of 21%. Haga (1959), in a similar study on another population, estimated the mortality due to incompatibility of heterozygotes to be about 5% and suggested that the difference between his findings and those of Matsunaga and Itoh might, in part, be explained on the basis of differences in living conditions. In a third study, Hiraizumi (1965) found no evidence for the elimination of children due to ABO incompatibility and pointed out that there might be an environmental factor involved in reduced fertility associated with ABO incompatibility. The living conditions were more favorable in the area he studied than in those studied by Matsunaga and Itoh or Haga, and this may have reduced the effects of incompatibility. It would appear that these effects may be quite sensitively modified by the environment and that harsh primitive conditions would lead to increased reproductive wastage, as Wood has suggested.

There are some additional aspects of relationships between malaria and blood groups which may be pertinent here. Oliver-Gonzalez and Torregrossa (1944) found that patients of groups O and B with chronic malaria had extremely high anti-A titers and suggested that the malarial parasite contains an A-like antigenic substance. If the presence of this A-like substance in (on) the parasite has any effect on the ability of a patient to resist malaria, one would expect to find high frequencies of O and B, and low frequencies of A, in areas where malaria is endemic. Athreya and Coriell (1967) showed that there is a correlation between high B allele frequencies and malarial endemicity, but that the frequency of the O allele is not elevated in these areas. This may be due, in part, to the preference of the malarial vector to feed on group-O individuals, as shown by Wood, in this way selecting against the O allele.

by EUGEN STROUHAL

Prague, Czechoslovakia. 26 VIII 74

The results of the experiments by Wood suggest that there really is a preference on for the part of mosquitoes for blood meals and landings on group-O subjects. Nevertheless, all other possible human physiological variables which might affect the mosquitoes' choice should be checked as well. The author has examined skin pigmentation, age, sex, skin temperature, degree of subcutaneous fat, and relative nutritional status. I would suggest including as well different biochemical properties of the blood, e.g., glycaemia, lipaemia, cholesterolaemia, as well as the *p*H of the blood and other features. Excluding all other possible dependencies of the mosquitoes' preference, one could consider the ABO blood groups' differential dependence unbiased.

The conclusion that malaria vectors favor enhanced survival for genes A and B and thus counterbalance the natural selection against these genes caused by mother-child ABO incompatibility would be of great general importance for blood-group research in anthropology. The ABO polymorphism would, accordingly, be considered primarily as the result of adaptive selection, reflecting more the ecological situation than the relationship between populations of common origin. In the case of the American Indians, the explanation that the overwhelming group-O frequency is the result of mother-child incompability operating in the absence of malaria vectors' influence seems to be in excellent agreement with earlier indications of the late introduction of malaria into the New World. But would it be possible to use the same explanation in other instances of high frequency of group O compiled, e.g., by Mourant (1954)? It would perhaps suit the extreme West European area (Wales, Scotland, Ireland, Iceland), the Caucasus, and the desert Bedouins of the Middle East or the Berbers of North Africa. But what about similar conditions found among the Sardinians, Cretans, or Subsaharan Negroes, living for millennia within the malarial zone? This question should be throughly studied in order to see whether the agreement in the case of the American Indians is not only accidental and whether the counterbalance between malaria vectors' choice and mother-child ABO incompatibility could generally explain the ABO polymorphism. It seems, however, that malaria vectors are not the only factor acting against the mother-child incompatibility.

Reply

by CORINNE SHEAR WOOD

Fullerton, Calif., U.S.A. 25 IX 74

I am very grateful to the respondents for their generally supportive and consistently provocative comments. In particular, I am gratified to find the recurrent theme, which I heartily endorse, that the findings of this one study should be followed by additional studies of the relationship between host preference of disease vectors and the blood groups of their hosts.

Angel raises the question of the varying levels of pathogenicity of the different *Plasmodia*. There is no doubt that

falciparum is the most virulent, particularly in unadapted populations; however, I think that he would not oppose the probability that at least *P. vivax* and *P. malariae,* perhaps not *P. ovale,* in the course of human history would have figured significantly in child loss as well as in reduced vigor and health in unprotected adults such that the reproductive rates would have been affected.

Clabeaux, McCracken, and Salzano question the composition of the test sample in regard to skin pigmentation, age, sex, skin temperature, ethnic composition, and nutritional status. A detailed account of the testing procedures with respect to these variables is presented in the more complete report which should appear shortly in *Human Biology.* Briefly, however, I would point out that the original purpose of the investigation was to examine mosquito choices as related to varying degrees of host pigmentation; the use of contrasting ABO subjects was instituted in order to have a clear marker of precisely which subject actually gave the blood meal. Preliminary findings suggested a trend of preference for lighter skin colors; however, insufficient numbers of varying subjects were available satisfactorily to pursue the question. With little more than a strong intuitive bias, I am most anxious to subject the skin-pigmentation factor to additional, controlled study. The other factors were examined statistically and showed no selection preference.

The factor of soaps, colognes, and perfumes used by the subjects, queried by McCracken, was, I hope, eliminated by routinely having the volunteers wash both arms in the laboratory using the same soap and water before each test. Further, the simulated tropical conditions and the ten-minute initial "warm-up" period rapidly reduced each subject and observer to similar degrees of sweat production, which acted as a great neutralizer.

Durbin adds a fascinating archaeological contribution and in the process answers the question of whether the possession of only O genes gave the American Indians increased resistance to various diseases, as suggested by Livingstone. He states, as do many historians (cf. Boyd 1941, Effertz 1909), that when virulent microorganisms were introduced, there was a striking degree of susceptibility among the aboriginal populations. Not only malaria, but cholera, yellow fever, smallpox, measles, etc., struck cataclysmic blows.

Goldstein and Salzano raise several questions, particularly, how the mosquito would know which person had which blood group. I am unable to answer this, nor do I know why some mosquitoes have evolved a strong zoophilic preference while others are anthropophilic in their host choices. The phenomenon of host specificity has been a perplexing problem for many biological investigators. I am not familiar with any answer to the question "How do they know?" If, indeed, the mosquitoes prefer one blood group to another, the terminal sugars added to the parent "H" substance, N-acetylglactosamine in the case of A and D-galactose in the case of B (Watson 1966), would be likely candidates for recognition signals. But of what advantage to the anopheline is one type of blood rather than another? It is known that the blood is required for egg production, and I have begun an investigation of the numbers of viable eggs laid as related to the blood-meal source. This work has only gotten off the ground, using the facilities generously offered by Drs. Maibach, Petrakis, and Khan of the University of California Medical Center in San Francisco. Unfortunately, the research failed to receive funding and must, therefore, move at the snail's pace determined by academic holidays and intersessions.

Hall's query regarding varying behavior between infected and uninfected anophelines is certainly legitimate, but is unanswerable because of the ethical considerations involved. Although many similar questions in the past were resolved using human subjects for disease studies (e.g., Jenner's young neighbor boy, who was given vaccinia, Laveran's son, who accepted *Plasmodia,* and many more), today investigations which deliberately expose human volunteers to infected material are precluded by the ethics of responsible workers.

Hoffman, Livingstone, Pollitzer, and Salzano quite correctly propose that, for a direct study of American malaria vectors, *A. darlingi, A. punctipennis,* and *A. quadrimaculatus* would have been the mosquitoes of choice. Here again, only further investigation can supply answers to their question. *A. gambiae* was used simply because it was available and is relatively amenable to laboratory breeding.

Hoffman asks, "What if the *Plasmodia* . . . had a predilection for blood-types A, B, and AB?" While this is an intriguing question in itself, I believe it involves a quite separate field of investigation. There may indeed be different rates of proliferation in recipients of varying blood groups, just as there are in persons with hemoglobin S, thalassemia, G-6-P-D deficiency, etc. Nevertheless, I question his charge of "*non sequitur.*" The *Plasmodia* must first be introduced into the human bloodstream by the bite of an infected mosquito. This initial step in the complicated cycle is the only one for which I offer any evidence, but the importance of the initial choice of host in the epidemiology of malaria should not be underestimated.

Livingstone's argument that "epidemic malaria or malaria with low endemicity may actually cause more mortality than highly endemic malaria" appears to me to support rather than negate the paper's proposal. As I pointed out, resistance is acquired primarily through continuous, moderate exposure. Under these conditions, group-A and group-B persons ideally would receive sufficient infections to initiate and maintain some immunological response, whereas in an epidemic situation the time factor required for the process to be completed would be absent.

Likewise, McCracken's "in terms of mortality or impaired reproductivity, what is the difference between a blood-meal mean of 4.87 for blood-group O and 3.50 . . . for blood-group A . . .?" misses the point of the dynamics of immunological response to malaria. The difference may be precisely that which is required to initiate and maintain immunological response at one level, but overwhelming at a level somewhat higher, particularly when one considers that each of the initial *Plasmodia* injected rapidly multiplies many thousandfold once in the human body. For each injected sporozoite, as many as 30,000 merozoites may be the end product of the exoerythrocytic and erythrocytic phases (cf. Bates 1965, MacDonald 1957). The human body as a rule will not survive infections of 20% or more of its red cells. The 4.87 and 3.50, therefore, must be seen in terms of numbers of subsequent red-cell-destroying merozoites, and the difference may be critical, particularly in the infant or young child.

I agree wholeheartedly with Meiklejohn and Strouhal, who point out that the "rather complex geographic patterning of ABO frequencies in areas of the Old World *not* subject to malaria" raises many questions. Here I would suspect that vector-borne diseases such as bubonic plague, typhus, yellow fever, and others may have been critical factors. Has anyone ever examined the host preferences of the rat fleas implicated as bearers of *Pasteurella pestis,* or the lice responsible for typhus? I have begun a study of *Aedes aegypti,* the yellow-fever vector, but much more needs to be done on this big question. Similarly, Mourant and Salzano note the strange pockets of high group-A genes among such populations as the Blackfeet and related tribes located in small areas of the New World. I would point to the fact that they coincide remarkably with the tick-borne rickettsiae, which transmit Rocky Mountain

spotted fever. Has the tick been an agent of selection in these areas?

Without question, as Strouhal and McCullough state, malaria vectors are not the only factors acting against mother-child ABO incompatibility. The basic point is that if, as my findings suggest, they are a factor, there is a crying need to examine all vectors of human diseases for the roles they may have played in the maintenance of unexplained polymorphisms—not only ABO, but the many other blood groups and secretor statuses as well. As McCullough, Mourant, and others imply, the findings rather beg interesting questions than provide answers.

I am especially grateful to Mourant for providing several literature sources with which I was not familiar, sources which examine the association between blood groups and malaria. Their findings of no significant difference in ABO distribution from control populations seem to lend substance to the claim that some other selection factor or factors has been in operation.

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