DISEASES OF THE TROPICS

BY

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TO THE MEMORY

OF

FREDERICK CHEEVER SHATTUCK, M.D.

His vision, energy and generosity led to the establishment of postgraduate teaching in tropical medicine at the Harvard Medical School in 1913. Its value was demonstrated in the First and Second World Wars.

PREFACE

Modern war and travel have increased the contact between the temperate and tropical regions to such an extent that a knowledge of the diseases of the tropics is no longer the province only of the specialist in that field. A working knowledge of the prevalent tropical diseases has become necessary to the medical student and to the general practitioner.

The primary objective in the preparation of this book has been to offer at moderate cost a concise but comprehensive account of the diseases of the tropics. The maladies of major importance have been described in considerable detail whereas those of lesser importance have been dealt with more or less briefly. Malaria, yaws, leishmaniasis, amebiasis, the typhus fevers, yellow fever, plague and cholera have been stressed.

The book should be of service to those who are concerned with public health programs because epidemiology, prevention and control are outlined for each disease. The newer diagnostic technics are described in detail. Many recent advances in treatment with the sulfonamides, with aureomycin, chloromycetin (chloramphenicol), with other antibiotics and with various remedies are described.

The illustrations were selected carefully for graphic qualities and the tabulated data present significant material in compact form. The systematic arrangement of the text and the comprehensive index are planned for ease of reference.

The list of references at the end of each chapter should be of great value to the reader who seeks additional knowledge of the tropical maladies.

I wish to express my appreciation to Doctors Donald L. Augustine, Joseph C. Bequaert, Emmett Reid Dunn, and Henry S. Fuller for their valuable contributions to this volume. I am indebted also for advice to a number of other colleagues at Harvard; namely, F. Sargent Cheever, Quentin M. Geiman, John E. Gordon, John H. Hanks, D. Mark Hegsted, John C. Snyder and Constantin P. Yaglou. Mrs. Tilton S. Bell and Mrs. William R. Mulvey have been most helpful in preparing the manuscript and have carefully checked the references.

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PROTOZOA OF THE BLOOD AND TISSUES

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HISTORY AND DISTRIBUTION OF MALARIA

Nomenclature and Definition. The term malaria is of Italian origin. In some of the older English medical text books malaria is called intermittent fever, or fever and ague. Other names are: paludisme, French; paludismo, Spanish; wechselfieber, German; koorts, Dutch.

Malaria is an infection which may exhibit a characteristic febrile reaction in man. The disease is acquired through the bite of a mosquito which is infected by parasites of the class Sporozoa, the order Haemosporidia and the family Plasmodidae. The genus *Plasmodium* is the only genus in this family. Besides the several species of *Plasmodium* which cause malaria in man, there are others which are peculiar to primates or to birds. Although two of the plasmodia of primates have been successfully inoculated into man, it has not been shown that any of the species peculiar to primates or birds are ever concerned in the causation of human malaria under natural conditions. Four species of plasmodia can cause malaria in man:

Plasmodium falciparum—falciparum malaria or malignant tertian malaria.
Plasmodium malariae—quartan malaria.
Plasmodium vivax—vivax malaria or benign tertian malaria.
Plasmodium ovale—ovale malaria is similar to vivax malaria.

Early History. Hippocrates, in the fifth century B.C., described several types of fever which must have been of malarial origin. The prevalence of malaria seems to have increased thereafter. The decline of the civilizations of ancient Greece, between 500 and 300 B.C., and of Rome, at a later date, has been ascribed in large measure to the depredations of malaria.

From very early times an association was recognized between the effluvia of marshes and the prevalence of malaria. Empedocles of Agrigentum, about 550 B.C., is supposed to have controlled an epidemic of malaria in Sicily by draining marshes and changing the courses of two rivers. Russell quoted Matthew Arnold to the effect that Empedocles was able to "cleanse to sweet airs the breath of poisonous streams."

Varro (128-116 B.C.), in *Rerum Rusticarum,* expressed the opinion that if you locate a villa near a river, you must take care to see if there are any marshes near it "because small, living beings swarm there, too small for the eyes to see, and get into the air and so on to the inside of the body through the mouth and nostrils and are the cause of obstinate diseases."

A few years later Columella said in his *Rei Rusticae* (about A.D. 25-50), "The (marsh) throws off a baleful stench in hot weather and breeds insects armed with

annoying stings, which attack us in dense swarms; then too it sends forth plagues of swimming and crawling things deprived of their winter moisture, and infected with poison by the mud and decaying filth from which we often contract mysterious diseases whose causes are ever beyond the understanding of physicians. . . ."

The theory of miasmata arising from marshes was re-examined and discussed at length by the great Italian physician, Lancissi, in his *De Noxiis Paludum Effluviis* published in 1717. Some passages in his book indicate that he believed the poison which causes malaria was inorganic but in other passages he said that minute living organisms or the eggs of insects can be carried through the air from the swamps and may gain entrance into the body by inhalations, or through external wounds, or that they may be ingested with food or water.

According to Paul F. Russell, Julius Caesar himself (first century B.C.) suffered from "intermittent fever," and the health of Caesar's army was shattered by this disease during the Civil Wars of Rome. Similarly, a pestilence destroyed the army of Frederick Barbarossa at Rome in A.D. 1168. It is surmised that this disease also was malaria.

During the Middle Ages and thereafter, sufferers from malaria were commonly subjected to blood-letting, excessive purgation, and overdosing with mercury. The introduction into Europe of cinchona in the form of powdered bark, by the Jesuits in the sixteen-thirties, led to prolonged and bitter controversies. Gradually it became recognized that fevers could be divided into two classes; namely, those which yield to cinchona and those which do not, and that the fevers which yield to cinchona are of intermittent or remittent type. Heroic methods of treatment for the intermittent fevers were superseded by the use of cinchona and later by its alkaloid, quinine.

Subsequent History. The history of malaria since the Middle Ages was sifted by Hirsch (1883). He said that epidemic malaria was widespread in Europe in 1557 and 1558 but that there is little reliable information about its prevalence in the sixteenth and seventeenth centuries. An epidemic occurred in the latter part of the seventeenth century and epidemics of malaria occurred in Europe at frequent intervals in the eighteenth century. Early in the nineteenth century epidemics were reported in India. Still later there was a reduction in the prevalence of malaria not only in Europe but also in the United States of America with coincident diminution in the severity of the disease.

Hirsch discussed in a masterly manner the epidemiology of malaria as known in the nineteenth century before the discovery of the parasite or of the mode of transmission of the disease.

The perfecting of the microscope by Antonj van Leeuwenhoek (1632-1723) and its use by him for studying the blood, the publication by Virchow in 1858 of his *Cellular Pathologie,* and use of the aniline dyes by Ehrlich for staining the blood cells, prepared the way for the discovery of the malaria parasite by Laveran of Paris in 1880. Laveran's discovery did not at once receive general acceptance because *Bacillus malariae* which had been cultivated from water and soil by Klebs and Crudeli (1879) was under consideration.

Malaria research was subsequently dominated for a number of years by a series of brilliant Italian investigators. Prominent among them were Marchiafava, Celli, Golgi, Grassi and Bignami. The parasites were described in greater detail in 1885 by

Marchiafava and Celli. Golgi showed that the malarial paroxysm is coincident with segmentation (1886) and he distinguished the quartan from the tertian parasite (1889). At about the same time the asexual cycle was worked out and Marchiafava and Celli recognized the differences between the tertian, the quartan and the malignant tertian parasites.

Romanovsky's blood stain was introduced in 1890. Grassi and Feletti studied "malaria" in birds in 1891. The process of exflagellation had been known for some time but had been misinterpreted until MacCallum observed conjugation of *Halteridium* in the blood of crows. Shortly afterward he saw the same phenomenon in blood from a case of falciparum malaria. These observations were reported together by MacCallum in 1897. In the following year Bastianelli, Bignami and Grassi discovered zygotes of parasites of human malaria in *Anopheles*.

Meanwhile, in 1894, Manson interested Ross in his hypothesis that malaria might be transmitted by mosquitoes. The theories involved in Manson's idea led Ross to initiate his studies which culminated in the transfer of malaria (*P. praecox*) from infected to healthy sparrows by the bite of *Culex* in 1897-98.

After this great demonstration by Ross, similar evidence for the transmission of malaria from man to man by *Anopheles* was brought forward by Bignami and his colleagues Bastianelli and Grassi in 1898. In 1900, Low, Sambon and Terzi lived for three months in a screened hut in the Roman Campagna at the height of the malaria season. They did not contract the disease. At about this time infected mosquitoes were sent by Bastianelli from Rome to London where they were fed by Manson upon two healthy volunteers. After an incubation period of two weeks both volunteers developed malaria. This experiment finally convinced the doubters.

History in the Americas. Carter (1931) believed that malaria did not exist in the Americas before the coming of Europeans. The Spanish conquerors doubtless brought the benign tertian parasite with them in their blood and they may also have imported the other forms in the same way during the late fifteenth century and early in the sixteenth century. It is safe to assume that the reservoir of infection was greatly increased in the latter part of the sixteenth century when Negro slaves were being imported in large numbers from Africa. *Plasmodium falciparum* may have been introduced in this way.

It has been suggested by Childs (1940) that malaria might have been an important cause of the remarkably rapid disappearance of the aborigines from the islands of the Caribbean Sea and from the low-lying parts of Mexico, Central and South America.

The English colony at Jamestown in Virginia suffered severely at an early date from a disease which may have been malaria, and Charleston, South Carolina, was heavily afflicted about 1680, some ten years after its founding.

Significance. Paul F. Russell (1943) has said: "What the actual sum total of malaria is today, no one knows, or can estimate closely. But one would venture to assume from such data as are available and from personal acquaintance with certain areas, that there are not less than 3,000,000 malaria deaths and at least 300,000,000 cases of malarial fevers each year, throughout the world. . . . In India, for example, malaria is a veritable juggernaut disease. There it kills at least a million persons every normal year, more in epidemic times. Another million die from indirect results

of malaria. Throughout all Hindustan there are each year at least 100,000,000 cases of malarial fevers. Quoting Sinton: 'There is no aspect of life in that country which is not affected, either directly or indirectly, by this disease. It constitutes one of the most important causes of economic misfortune, engendering poverty, diminishing the quantity and the quality of the food supply, lowering the physical and intellectual standard of the nation, and hampering increased prosperity and economic progress in every way.' "

The significance of malaria during World War II can scarcely be overemphasized.

Geographical Distribution. The approximate limits of distribution of indigenous malaria in the Eastern Hemisphere lie between 60° north and 35° south latitude. In the Americas, the limits lie roughly between 40° north and 35° south latitude.

Most of the regions of high endemicity lie between the Tropics of Cancer and Capricorn. More northerly foci of high endemicity are found in Italy, Albania, Greece, Macedonia, Palestine and the southern part of European Russia as well as in northern India.

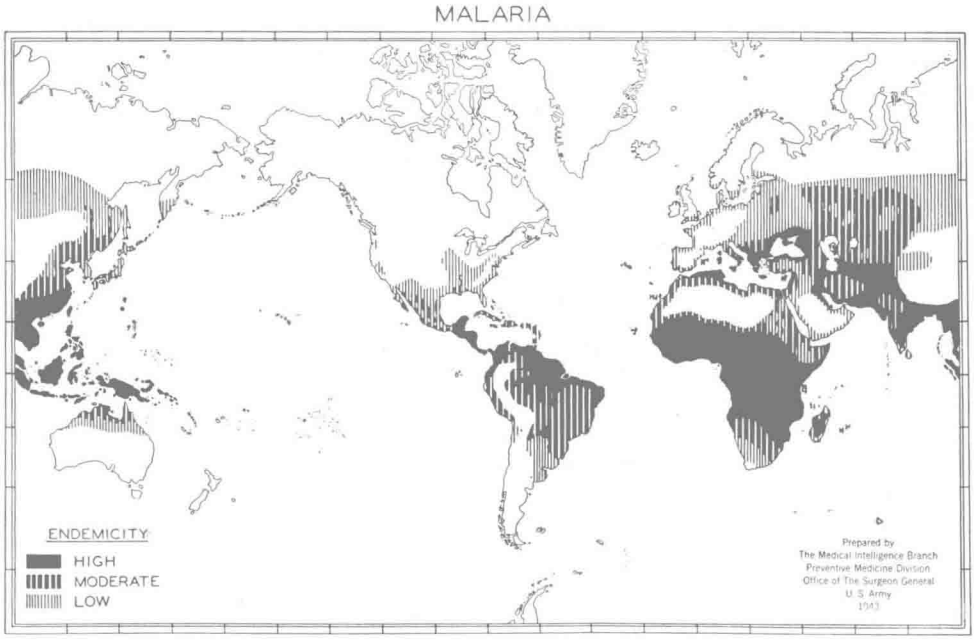

FIG. 1. WORLD DISTRIBUTION OF MALARIA.
(Courtesy of the Surgeon General, U.S. Army.)

In the Pacific Ocean there are many islands and archipelagos which formerly were, and perhaps still are, free from indigenous malaria. They are bounded on the east by a line which includes Juan Fernandez and the Galápagos Islands. Thence the line runs northwesterly around the Hawaiian Archipelago, Midway Island and Minamitori Shima. Turning southwesterly at the last point the line passes west of Minamitori Shima, Ogasawara Shoto and the Palau Islands. It then runs easterly to the Gilbert Islands where it takes an irregular southerly course which includes New

Caledonia and New Zealand. Thence it runs easterly back to Juan Fernandez. Many important groups of islands are found within this malaria-free area. Among them are Guam, the Marshalls, the Carolines, the Gilberts and the Ellice Islands, Samoa and Fiji (Fig. 3). In the Solomons and in New Guinea, on the other hand, malaria is highly endemic.

Malaria has invaded a number of tropical islands which used to be free from it. Well known examples are the islands of Mauritius and Réunion off the eastern coast of Africa, and Barbados in the West Indies.

Incidence. There is, as yet, no unit of measurement which serves adequately for comparing the incidence of malaria in the different parts of the world, because adequate morbidity and mortality statistics do not exist. This statement is true for all, or nearly all, of the countries in which malaria constitutes an important health problem, including the United States of America. Inadequacy of data is attributable to lack of confirmation of the diagnosis by blood examination or autopsy, to incomplete reporting of cases, or to absence of any system of reporting. Nevertheless, mortality rates for the United States and for a few other countries are of considerable value when due allowance is made for their defects.

Mortality rates based on total population within a political entity are apt to be strikingly low as compared with those for the regions of higher malaria incidence because the distribution of malaria is very uneven. The higher mortality rates are ascribable, as a rule, to *P. falciparum*. *P. vivax* and *P. malariae* cause relatively low mortalities even where they are very prevalent.

Among other indexes of the prevalence of malaria are morbidity rates, numbers of patients hospitalized for malaria, infection rates, attack rates, spleen rates (indexes) and parasite rates (indexes). The spleen rates and parasite rates or indexes (pages 39 and 40) are much used for determining approximately the proportion of infected individuals in a group or locality. The evaluation of data of this kind has been discussed in the chapter on control of malaria.

It is important to recognize that the incidence of malaria is not static. Before and until World War I, malaria in Europe had been declining spontaneously for many years. The incidence of malaria is subject to many influences some of which are known and others unknown. This aspect of the subject has been dealt with in the chapter on epidemiology of malaria.

The United States of America. The incidence of malaria in the various parts of the United States has fluctuated during periods of years. These fluctuations have been paralleled by changes in the extent of the endemic area. Boyd (1941) believed that, as a result of the development of rice culture on a large scale in the eighteenth century, the low lands of the Carolinas became the most intensely malarious regions of the Atlantic Coast.

The American Revolutionary War (1775-1783) intensified the incidence of malaria in parts of the Southern States. Westward migration of settlers was followed by a striking prevalence of malaria along the Mississippi River. During and after the War between the States (1860-1865) malaria increased markedly in many of the localities in which military operations had been conducted.

In the United States of America in the eighteen-sixties malaria was common along the northern tributaries of the Mississippi River, it extended to the Great Lakes and

even to parts of Canada. Subsequently, beginning about 1880, the incidence of malaria began to decrease in the northern part of the United States and in Canada. Gradually the endemic area receded until there was little indigenous malaria north of the Ohio River (Boyd, 1941).

Faust (1939) studied malaria death rates in the United States by counties for the period from 1933 to 1937 (Fig. 2). A comparatively small number of counties reported average rates as high as 50 or more per 100,000 of population. Rates between 25 and 49.9 were widely scattered but were confined to limited areas. On the other hand, rates below 25 prevailed throughout most of the endemic area.

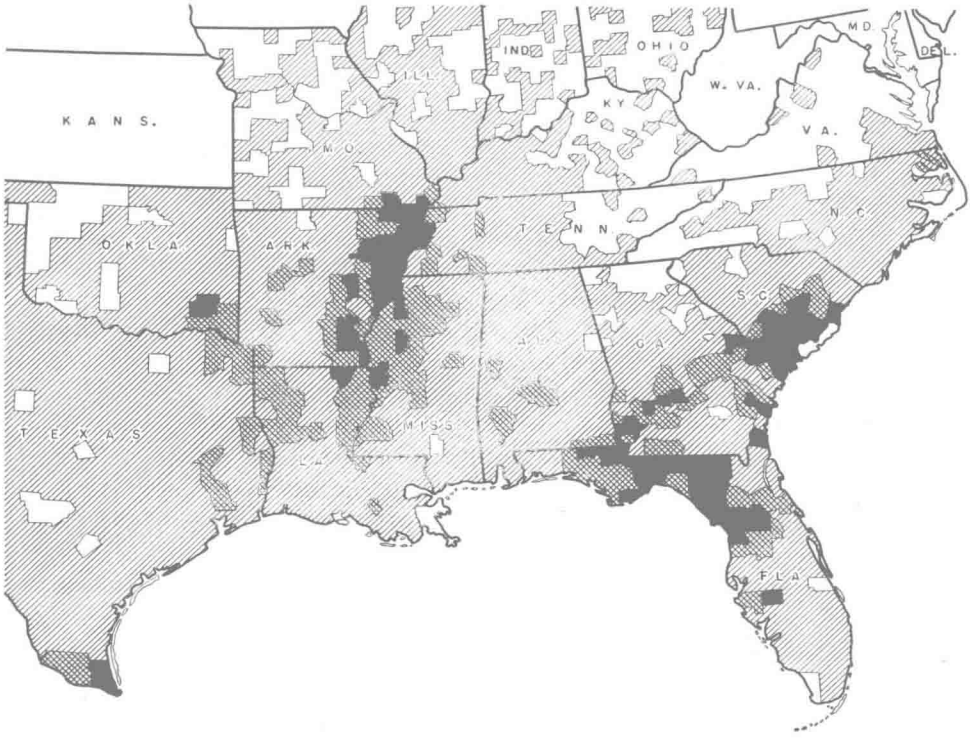

FIG. 2. DISTRIBUTION OF MALARIA MORTALITY IN THE UNITED STATES, 1933-1937.

The solid black indicates average rates of 50 or more deaths per 100,000; the cross hatch, rates from 25 to 49.9 per 100,000; and the diagonal lines, rates under 25 per 100,000. (Redrawn from Faust, in the *American Journal of Tropical Medicine*, 1939. Courtesy of Williams and Wilkins Co., Baltimore.)

Nearly all the counties of higher incidence, as indicated by the rates, were situated near the eastern seaboard in South Carolina, Georgia and Florida or along the Mississippi River in Missouri, Arkansas, Tennessee, and Mississippi. The exceptions were a single county in southeastern Oklahoma and another in southern Texas. Figure 2 emphasizes the unevenness of the distribution of malaria in the Southern States.

Vital statistics recently published by the United States Department of Commerce, Bureau of the Census 1943, show that death rates per 100,000 for malaria in the United States as a whole declined progressively from 3.7 in 1933 to 0.9 in 1941. The

death rates from malaria in 12 states in which malaria was most prevalent are shown in Table 1. A downward trend in most of the rates is evident in recent years. This trend has continued (Faust and others, 1946; and Andrews, 1948).

According to Watson and Hewitt (1941) indigenous malaria in the United States has been found in the Cumberland Mountains of Tennessee at 1200 feet (364 meters); in Reno, Nevada, at 4000 feet (1200 meters), in the valleys of the Rio Grande and San Juan Rivers in New Mexico at altitudes of 5,600 and 5,300 feet respectively (1,680 and 1,590 meters), and in California at 5,482 feet (1,644 meters). The vector at these altitudes in New Mexico and probably in California is *A. maculipennis*. This is a hardy species which is adaptable to northern latitudes and to the comparatively low temperatures incidental to altitude within the tropics.

Mexico, Central America and the West Indies. In parts of Mexico, Central America and the West Indies, malaria is far more common and more often fatal than in the United States of America. These higher death rates are due largely to greater prevalence of *P. falciparum*. On the basis of such data as were available, Faust (1941) prepared a map contrasting the malaria mortality rates for different parts of the region. Average death rates ranging from 1 to 100 per 100,000 were shown for the greater part of Mexico, but rates from 101 to 500 were widely distributed especially along the coasts. In some limited localities the rates ran up to 1,000 or even higher. The average for Mexico as a whole was 145.5 and for Guatemala 414. Figures for Honduras ranged from 200 to 744. Other countries in Central America showed intermediate rates. The rate for the cities of Panama and Colon taken together was only 29.1.

There has been no malaria in the Bermudas because of absence of a vector.

In the West Indies the death rates ranged from 268 for Haiti down to 15.2 for the Island of St. Vincent and 12.4 for Guadeloupe. Barbados, which used to be free from malaria because there was no vector, had a malaria death rate of 28.6 between 1927 and 1930. According to a report of the League of Nations Malaria Commission (1932), there was little malaria remaining in Barbados in 1929. Boyd observed that in Jamaica endemic malaria occurred chiefly at levels below 1,640 feet (500 meters).

In the islands of Trinidad and Tobago, Downs and others (1943) examined many thousand school children between the ages of 5 and 15 years. The spleen index was 8.4 per cent. Blood films showed falciparum to be the most common species of plasmodium. The quartan parasite was least frequently seen, except in certain localities in which it was more common than vivax. About half of Trinidad was free from malaria for lack of a vector in that region. The principal vectors found in Trinidad are *A. bellator* and *A. aquasalis*. In the Greater Antilles, Mexico and Central America *A. albimanus* is said to be the principal vector of malaria. It breeds chiefly at low altitudes but it is found up to elevations of 3,000 feet (900 meters). In the Lesser Antilles *A. tarsimaculatus* has a similar significance and a like distribution.

Many of the islands of the Caribbean Sea are mountainous in the interior. Indigenous malaria in these islands is found chiefly near the coast at levels of less than 500 feet (150 meters).

Malaria has been reported by Bustamente (1939) from Xochimilco on the plateau of Mexico at 6,792 feet (2,037 meters).

In Guatemala, *A. albimanus* transmits malaria up to about 3,200 feet (960 meters).

TABLE 1. DEATH RATES FOR MALARIA.

Rates are per 100,000 in 12 states of the United States of America by years for the period 1931 to 1941 inclusive and number of deaths from malaria in each state for the year 1941. In the other 17 of the 29 states which reported deaths from malaria during the period, the rates were very low.

State	Malaria deaths 1941	Rates										
		1941	1940	1939	1938	1937	1936	1935	1934	1933	1932	1931
Arkansas	159	8.2	9.1	13.4	19.1	20.1	21.4	30.0	31.7	47.1	24.7	25.9
Mississippi	150	6.9	8.0	10.7	12.7	14.8	17.2	25.4	33.1	39.2	19.5	12.6
So. Carolina	125	6.6	6.2	8.9	11.5	14.2	23.6	23.5	19.4	13.5	13.1	14.2
Florida	84	4.4	5.1	5.9	9.3	11.9	20.9	20.2	28.6	24.6	16.2	14.9
Alabama	123	4.3	7.3	7.0	8.0	7.8	12.5	11.6	10.7	9.8	6.7	8.0
Louisiana	77	3.3	3.7	4.8	8.0	7.9	10.9	15.9	16.2	19.4	7.2	7.0
Georgia	82	2.6	3.4	3.5	6.6	7.9	20.3	12.7	13.6	12.3	10.6	10.4
Texas	156	2.4	2.7	2.8	4.1	5.8	8.0	10.6	8.3	7.2	—	—
Oklahoma	53	2.3	1.3	2.0	3.8	3.9	4.0	5.8	5.8	5.6	4.5	4.3
Tennessee	53	1.8	2.2	3.6	3.9	3.8	5.6	7.9	9.5	10.0	4.9	5.4
No. Carolina	29	0.8	1.7	1.4	2.0	2.5	4.4	2.7	2.0	1.5	1.6	1.4
Missouri	25	0.7	1.0	1.8	2.0	2.4	2.8	4.4	5.0	5.3	3.1	4.0

(From U.S. Dept. of Commerce, Bureau of the Census. Summary of Vital Statistics, U.S. 1941. Jan. 5, 1943; vol. 18, no. 2; Vital Statistics, Special Reports, p. 12.)

At higher levels *A. pseudopunctipennis* is probably the principal vector and *A. hectoris* may be important in certain localities.

Malaria seems to be spreading along the river valleys into the Highlands. All three species of the parasite are found around Lake Atitlán, altitude 4,660 feet (1,554 meters). Vivax malaria may be endemic at somewhat higher levels because this parasite can develop at temperatures below those required for falciparum.

South America. Most of the available figures on the incidence of malaria in South America are of doubtful significance except those for certain limited regions in which surveys have been made. Data published by the League of Nations Malaria Commission (1932) indicate that death rates have ranged from 33 to 560 per 100,000 population and spleen rates from 0 to 85 per cent. Malaria is hyperendemic in many tropical parts of South America where rainfall is abundant and where the elevation of the country is moderate or low. This is notably true of Colombia, Venezuela, the Guianas, Brazil, Ecuador, Peru and Bolivia. High percentages of malarial infection doubtless occur in many Andean valleys within the tropical zone.

Ecuador. Malaria is prevalent near but below Quito at an elevation of about 8,500 feet (2,584 meters) (Dr. Hanson, personal communication). In the Chillos Valley, near Quito, which had been free from malaria, a serious outbreak occurred a few years ago. The altitude of the valley is about 7,500 feet (2,280 meters) (Dr. Roberto Nevárez, personal letter, 1944).

Bolivia. Malaria is transmitted in Bolivia by *A. pseudopunctipennis* (Hackett, 1945), and is prevalent in the mountain valleys at altitudes up to about 2,600 meters. An official report (1942) gave the following percentages of infection:

Cochabamba vicinity	28.84 per cent
Tanja vicinity	24.15 per cent
Chiquisaca vicinity	19.30 per cent
La Paz vicinity	15.41 per cent

Malaria was far less prevalent in the town of Cochabamba than in the surrounding country.

Brazil. The Oswaldo Cruz Commission (1913) saw very few individuals on the Rio Negro in Brazil who did not show signs of malaria, and C. Chagas (1921) pointed out that the severer forms of malaria were prevalent in the valley of the Amazon. Similar observations were made by Strong and his associates (1926) at Manaos on the Rio Negro and on the lower part of the Rio Branco (Amazonas, Brazil).

In a series of nearly 7,000 blood examinations made in Pará, Souza-Araujo (1923) found malaria parasites in 45.4 per cent. *P. falciparum* was present in 54 per cent and *P. vivax* in 46 per cent. Chagas reported the presence of quartan parasites from the Rio Acre and he attributed to them some cases of very severe malaria associated with rapidly increasing anemia.

In 1925, the writer was informed by Indians of an isolated tribe living far up the Rio Branco that they suffered from malaria only after visiting a ranch on the lower part of the river. The trip down river, a distance of about 200 miles by water, was made only once a year by a few members of the tribe. (Strong and others, 1926.)

The most menacing epidemic of malaria which has occurred in the New World within recent years followed the introduction of *Anopheles gambiae* into Natal in