

= History of malaria =

The history of malaria stretches from its prehistoric origin as a zoonotic disease in the primates of Africa through to the 21st century . A widespread and potentially lethal human infectious disease , at its peak malaria infested every continent , except Antarctica . Its prevention and treatment have been targeted in science and medicine for hundreds of years . Since the discovery of the parasites which cause it , research attention has focused on their biology , as well as that of the mosquitoes which transmit the parasites .

References to its unique , periodic fevers are found throughout recorded history beginning in 2700 BC in China .

For thousands of years , traditional herbal remedies have been used to treat malaria . The first effective treatment for malaria came from the bark of cinchona tree , which contains quinine . After the link to mosquitos and their parasites were identified in the early twentieth century , mosquito control measures such as widespread use of DDT , swamp drainage , covering or oiling the surface of open water sources , indoor residual spraying and use of insecticide treated nets was initiated . Prophylactic quinine was prescribed in malaria endemic areas , and new therapeutic drugs , including chloroquine and artemisinins , were used to resist the scourge .

Malaria researchers have won multiple Nobel Prizes for their achievements , although the disease continues to afflict some 200 million patients each year , killing more than 600 @,@ 000 .

Malaria was the most important health hazard encountered by U.S. troops in the South Pacific during World War II , where about 500 @,@ 000 men were infected . According to Joseph Patrick Byrne , " Sixty thousand American soldiers died of malaria during the African and South Pacific campaigns . "

At the close of the 20th century , malaria remained endemic in more than 100 countries throughout the tropical and subtropical zones , including large areas of Central and South America , Hispaniola (Haiti and the Dominican Republic) , Africa , the Middle East , the Indian subcontinent , Southeast Asia , and Oceania . Resistance of Plasmodium to anti @-@ malaria drugs , as well as resistance of mosquitos to insecticides and the discovery of zoonotic species of the parasite have complicated control measures .

= = Origin and prehistoric period = =

The first evidence of malaria parasites was found in mosquitoes preserved in amber from the Palaeogene period that are approximately 30 million years old . Human malaria likely originated in Africa and coevolved with its hosts , mosquitoes and non @-@ human primates . Malaria protozoa are diversified into primate , rodent , bird , and reptile host lineages . Humans may have originally caught Plasmodium falciparum from gorillas . P. vivax , another malarial Plasmodium species among the six that infect humans , also likely originated in African gorillas and chimpanzees . Another malarial species recently discovered to be transmissible to humans , P. knowlesi , originated in Asian macaque monkeys . While P. malariae is highly host specific to humans , there is spotty evidence that low level non @-@ symptomatic infection persists among wild chimpanzees .

About 10 @,@ 000 years ago , malaria started having a major impact on human survival , coinciding with the start of agriculture in the Neolithic revolution . Consequences included natural selection for sickle @-@ cell disease , thalassaemias , glucose @-@ 6 @-@ phosphate dehydrogenase deficiency , Southeast Asian ovalocytosis , elliptocytosis and loss of the Gerbich antigen (glycophorin C) and the Duffy antigen on the erythrocytes , because such blood disorders confer a selective advantage against malaria infection (balancing selection) . The three major types of inherited genetic resistance (sickle @-@ cell disease , thalassaemias , and glucose @-@ 6 @-@ phosphate dehydrogenase deficiency) were present in the Mediterranean world by the time of the Roman Empire , about 2000 years ago .

Molecular methods have confirmed the high prevalence of P. falciparum malaria in ancient Egypt . The Ancient Greek historian Herodotus wrote that the builders of the Egyptian pyramids (circa 2700 - 1700 BCE) were given large amounts of garlic , probably to protect them against malaria . The

Pharaoh Sneferu , the founder of the Fourth dynasty of Egypt , who reigned from around 2613 ? 2589 BCE , used bed @-@ nets as protection against mosquitoes . Cleopatra VII , the last Pharaoh of Ancient Egypt , similarly slept under a mosquito net . However , whether the mosquito nets were used for the purpose of malaria prevention , or for more mundane purpose of avoiding the discomfort of mosquito bites , is unknown . The presence of malaria in Egypt from circa 800 BCE onwards has been confirmed using DNA @-@ based methods .

= = Classical period = =

Malaria became widely recognized in ancient Greece by the 4th century BCE , and is implicated in the decline of many city @-@ state populations . The term ?????? (Greek for miasma) : " stain , pollution " , was coined by Hippocrates of Kos who used it to describe dangerous fumes from the ground that are transported by winds and can cause serious illnesses . Hippocrates (460 ? 370 BCE) , the " father of medicine " , related the presence of intermittent fevers with climatic and environmental conditions and classified the fever according to periodicity : Gk . : tritaios pyretos / L . : febris tertiana (fever every third day) , and Gk . : tetartaios pyretos / L . : febris quartana (fever every fourth day) .

The Chinese Huangdi Neijing (The Inner Canon of the Yellow Emperor) dating from ~ 300 BCE - 200 CE apparently refers to repeated paroxysmal fevers associated with enlarged spleens and a tendency to epidemic occurrence . Around 168 BCE , the herbal remedy Qing @-@ hao (??) (*Artemisia annua*) came into use in China to treat female hemorrhoids (Wushi 'er bingfang translated as " Recipes for 52 kinds of diseases " unearthed from the Mawangdui tombs) . Qing @-@ hao was first recommended for acute intermittent fever episodes by Ge Hong as an effective medication in the 4th @-@ century Chinese manuscript Zhou hou bei ji fang , usually translated as " Emergency Prescriptions kept in one 's Sleeve " . His recommendation was to soak fresh plants of the artemisia herb in cold water , wring it out and ingest the expressed bitter juice in its raw state .

'Roman fever ' refers to a particularly deadly strain of malaria that affected the Roman Campagna and the city of Rome throughout various epochs in history . An epidemic of Roman fever during the fifth century AD may have contributed to the fall of the Roman empire . The many remedies to reduce the spleen in Pedanius Dioscorides 's *De Materia Medica* have been suggested to have been a response to chronic malaria in the Roman empire .

In 835 , the celebration of Halloween was moved from May to November at the behest of Pope Gregory IV , on the " practical grounds that Rome in summer could not accommodate the great number of pilgrims who flocked to it " , and perhaps because of public health considerations regarding Roman Fever , which claimed a number of lives of pilgrims during the sultry summers of the region .

= = Middle Ages = =

During the Middle Ages , treatments for malaria (and other diseases) included blood @-@ letting , inducing vomiting , limb amputations and trepanning . Some turned to witchcraft and astrology . Physicians and surgeons as well as folk @-@ healers administered ineffective and often deadly herbs - Belladonna , for example .

= = = European Renaissance = = =

The name malaria derived from mal aria (' bad air ' in Medieval Italian) . This idea came from the Ancient Romans who thought that this disease came from the horrible fumes in the swamps . The word malaria has its roots in the miasma theory , as described by historian and chancellor of Florence Leonardo Bruni in his *Historiarum Florentini populi libri XII* , which was the first major example of Renaissance historical writing :

Avuto i Fiorentini questo fortissimo castello e fornitolo di buone guardie , consigliavano fra loro medesimi fosse da fare . Erano alcuni a ' quali pareva sommamente utile e necessario a ridurre lo

esercito , e massimamente essendo affaticato per la infermità e per la mala ariae per lungo e difficile campeggiare nel tempo dell 'autunno e in luoghi infermi , e vedendo ancora ch 'egli era diminuito assai per la licenza concessuta a molti pel capitano di potersi partire : perocchè , nel tempo che eglino erano stati lungamente a quello assedio , molti , o per disagio del campo o per paura d 'infermità , avevano domandato e ottenuto licenza da lui (Acciajuoli 1476) .

After the Florentines had conquered this stronghold , after putting good guardians on it they were discussing among themselves how to proceed . For some of them it appeared most useful and necessary to reduce the army , more so as it was extremely stressed by disease and bad air , and due to the long @-@ lasting and difficult camps in unhealthy places during the autumn . They (the Florentines) further considered that the army was reduced in numbers due to the leave permits granted to many soldiers by their officers . In fact , during the siege , many soldiers had asked and obtained leave permits due to the camp hardships and fear of illness [translated from medieval Italian , Toscanic dialect] .

The coastal plains of southern Italy fell from international prominence when malaria expanded in the sixteenth century . At roughly the same time , in the coastal marshes of England , mortality from " marsh fever " or " tertian ague " (ague : via French from medieval Latin *acuta* (*febris*) , acute fever) was comparable to that in sub @-@ Saharan Africa today . William Shakespeare was born at the start of the especially cold period that climatologists call the " Little Ice Age " , yet he was aware enough of the ravages of the disease to mention it in eight of his plays .

Medical accounts and ancient autopsy reports state that tertian malarial fevers caused the death of four members of the prominent Medici family of Florence . These claims have been confirmed with more modern methodologies .

= = Spread to the Americas = =

Malaria was not referenced in the " medical books " of the Mayans or Aztecs . European settlers and their West African slaves likely brought malaria to the Americas in the 16th century .

In the book ? 1493 , ? the author Charles Mann , cites sources that speculate that the reason African slaves were brought to the British Americas was because of their immunity to malaria . Britain did not have large number of African slaves , there were plenty of unemployed workers who could come as indentured servants . In the area above the Mason @-@ Dixon line , the malaria protozoa did not fare well , the English @-@ speaking indentured servant proved more profitable as he would work toward his freedom and hence worked with less supervision and coercion . As malaria spread , places such as the tidewater of Virginia and South Carolina which had previously been habitable by white people became endemic with malaria . Small white landholders were at a disadvantage to plantation owners , as they risk complete economic ruin when they were sick , while plantation owners relied on more malaria resistant West African slaves . Malaria caused huge losses to British forces in the South during the revolutionary war as well as to Union forces during the Civil War . Malaria also helped weaken the native American population and make them more susceptible to other diseases .

= = Cinchona tree = =

Spanish missionaries found that fever was treated by Amerindians near Loxa (Peru) with powder from Peruvian bark (later established to be from any of several trees of genus *Cinchona*) . It was used by the Quechua Indians of Peru to reduce the shaking effects caused by severe chills . Jesuit Brother Agostino Salumbrino (1561 ? 1642) , who lived in Lima and was an apothecary by training , observed the Quechua using the bark of the cinchona tree for that purpose . While its effect in treating malaria (and hence malaria @-@ induced shivering) was unrelated to its effect in controlling shivering from cold , it was nevertheless effective for malaria . The use of the ? fever tree ? bark was introduced into European medicine by Jesuit missionaries (Jesuit 's bark) . Jesuit Bernabé de Cobo (1582 ? 1657) , who explored Mexico and Peru , is credited with taking cinchona bark to Europe . He brought the bark from Lima to Spain , and then to Rome and other parts of Italy

, in 1632 . Francesco Torti wrote in 1712 that only ? intermittent fever ? was amenable to the fever tree bark . This work finally established the specific nature of cinchona bark and brought about its general use in medicine .

It would be nearly 200 years before the active principles , quinine and other alkaloids , of cinchona bark were isolated . Quinine , a toxic plant alkaloid , is , in addition to its anti @-@ malarial properties , an effective muscle relaxant , as the modern use for nocturnal leg cramps suggests (corroborating its use for shivering by the Peruvian Indians) .

= = = Clinical indications = = =

In 1717 , the dark pigmentation of a postmortem spleen and brain was published by the epidemiologist Giovanni Maria Lancisi in his malaria text book *De noxiis paludum effluviis eorumque remediis* . This was one of the earliest reports of the characteristic enlargement of the spleen and dark color of the spleen and brain which are the most constant post @-@ mortem indications of chronic malaria infection . He related the prevalence of malaria in swampy areas to the presence of flies and recommended swamp drainage to prevent it .

= = 19th century = =

In the nineteenth century , the first drugs were developed to treat malaria and parasites were first identified as its source .

= = = Antimalarial drugs = = =

= = = = Quinine = = = =

French chemist Pierre Joseph Pelletier and French pharmacist Joseph Bienaimé Caventou separated in 1820 the alkaloids cinchonine and quinine from powdered fever tree bark , allowing for the creation of standardized doses of the active ingredients . Prior to 1820 , the bark was simply dried , ground to a fine powder and mixed into a liquid (commonly wine) for drinking .

An English trader , Charles Ledger , and his Amerindian servant spent four years collecting cinchona seeds in the Andes in Bolivia , highly prized for their quinine but whose export was prohibited . Ledger managed to get seeds out ; in 1865 , the Dutch government cultivated 20 @,@ 000 trees of the *Cinchona ledgeriana* in Java (Indonesia) . By the end of the nineteenth century , the Dutch had established a world monopoly over its supply .

= = = = ' Warburg 's Tincture ' = = = =

In 1834 , in British Guiana , a German physician , Carl Warburg , invented an antipyretic medicine : ' Warburg 's Tincture ' . This secret , proprietary remedy contained quinine and other herbs . Trials were made in Europe in the 1840s and 1850s . It was officially adopted by the Austrian Empire in 1847 . It was considered by many eminent medical professionals to be a more efficacious antimalarial than quinine . It was also more economical . The British Government supplied Warburg 's Tincture to troops in India and other colonies .

= = = = Methylene blue = = = =

In 1876 , methylene blue was synthesized by German chemist Heinrich Caro . Paul Ehrlich in 1880 described the use of " neutral " dyes ? mixtures of acidic and basic dyes for the differentiation of cells in peripheral blood smears . In 1891 Ernst Malachowski and Dmitri Leonidovich Romanowsky independently developed techniques using a mixture of Eosin Y and modified methylene blue (methylene azure) that produced a surprising hue unattributable to either staining component : a

shade of purple . Malachowski used alkali @-@ treated methylene blue solutions and Romanowsky used methylene blue solutions which were molded or aged . This new method differentiated blood cells and demonstrated the nuclei of malarial parasites . Malachowski 's staining technique was one of the most significant technical advances in the history of malaria .

In 1891 , Paul Guttman and Ehrlich noted that methylene blue had a high affinity for some tissues and that this dye had a slight antimalarial property . Methylene blue and its congeners may act by preventing the biocrystallization of heme .

= = = Etiology : Identification of Plasmodium and Anopheles = = =

In 1848 , German anatomist Johann Heinrich Meckel recorded black @-@ brown pigment granules in the blood and spleen of a patient who had died in a mental hospital . Meckel was thought to have been looking at malaria parasites without realizing it ; he did not mention malaria in his report . He hypothesized that the pigment was melanin . The causal relationship of pigment to the parasite was established in 1880 , when French physician Charles Louis Alphonse Laveran , working in the military hospital of Constantine , Algeria , observed pigmented parasites inside the red blood cells of malaria sufferers . He witnessed the events of exflagellation and became convinced that the moving flagella were parasitic microorganisms . He noted that quinine removed the parasites from the blood . Laveran called this microscopic organism *Oscillaria malariae* and proposed that malaria was caused by this protozoan . This discovery remained controversial until the development of the oil immersion lens in 1884 and of superior staining methods in 1890 ? 1891 .

In 1885 , Ettore Marchiafava , Angelo Celli and Camillo Golgi studied the reproduction cycles in human blood (Golgi cycles) . Golgi observed that all parasites present in the blood divided almost simultaneously at regular intervals and that division coincided with attacks of fever . In 1886 Golgi described the morphological differences that are still used to distinguish two malaria parasite species *Plasmodium vivax* and *Plasmodium malariae* . Shortly after this Sakharov in 1889 and Marchiafava & Celli in 1890 independently identified *Plasmodium falciparum* as a species distinct from *P. vivax* and *P. malariae* . In 1890 , Grassi and Feletti reviewed the available information and named both *P. malariae* and *P. vivax* (although within the genus *Haemamoeba* .) By 1890 , Laveran 's germ was generally accepted , but most of his initial ideas had been discarded in favor of the taxonomic work and clinical pathology of the Italian school . Marchiafava and Celli called the new microorganism *Plasmodium* . *H. vivax* was soon renamed *Plasmodium vivax* . In 1892 , Marchiafava and Bignami proved that the multiple forms seen by Laveran were from a single species . This species was eventually named *P. falciparum* . Laveran was awarded the 1907 Nobel Prize for Physiology or Medicine " in recognition of his work on the role played by protozoa in causing diseases " .

Dutch physician Pieter Pel first proposed a tissue stage of the malaria parasite in 1886 , presaging its discovery by over 50 years . This suggestion was reiterated in 1893 when Golgi suggested that the parasites might have an undiscovered tissue phase (this time in endothelial cells) . Pel in 1896 supported Gogli 's latent phase theory .

The establishment of the scientific method from about the mid @-@ 19th century on demanded testable hypotheses and verifiable phenomena for causation and transmission . Anecdotal reports , and the discovery in 1881 that mosquitos were the vector of yellow fever , eventually led to the investigation of mosquitos in connection with malaria .

An early effort at malaria prevention occurred in 1896 in Massachusetts . An Uxbridge outbreak prompted health officer Dr. Leonard White to write a report to the State Board of Health , which led to a study of mosquito @-@ malaria links and the first efforts for malaria prevention . Massachusetts state pathologist , Theobald Smith , asked that White 's son collect mosquito specimens for further analysis , and that citizens add screens to windows , and drain collections of water .

Britain 's Sir Ronald Ross , an army surgeon working in Secunderabad India , proved in 1897 that malaria is transmitted by mosquitoes , an event now commemorated via World Mosquito Day . He was able to find pigmented malaria parasites in a mosquito that he artificially fed on a malaria patient who had crescents in his blood . He continued his research into malaria by showing that

certain mosquito species (*Culex fatigans*) transmit malaria to sparrows and he isolated malaria parasites from the salivary glands of mosquitoes that had fed on infected birds . He reported this to the British Medical Association in Edinburgh in 1898 .

Giovanni Battista Grassi , professor of Comparative Anatomy at Rome University , showed that human malaria could only be transmitted by *Anopheles* (Greek *anofelis* : good @-@ for @-@ nothing) mosquitoes . Grassi along with coworkers Amico Bignami , Giuseppe Bastianelli and Ettore Marchiafava announced at the session of the Accademia dei Lincei on 4 December 1898 that a healthy man in a non @-@ malarial zone had contracted tertian malaria after being bitten by an experimentally infected *Anopheles claviger* specimen .

In 1898 @-@ 99 , Bastianelli , Bignami and Grassi were the first to observe the complete transmission cycle of *P. falciparum* , *P. vivax* and *P. malaria* from mosquito to human and back in *A. claviger* .

A dispute broke out between the British and Italian schools of malariology over priority , but Ross received the 1902 Nobel Prize for Physiology or Medicine for " his work on malaria , by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and methods of combating it " .

= = = Synthesis of quinine = = =

William Henry Perkin , a student of August Wilhelm von Hofmann at the Royal College of Chemistry in London , unsuccessfully tried in the 1850s to synthesize quinine in a commercial process . The idea was to take two equivalents of N @-@ allyltoluidine (C

10H

13N) and three atoms of oxygen to produce quinine (C

20H

24N

2O

2) and water . Instead , Perkin 's mauve was produced when attempting quinine total synthesis via the oxidation of N @-@ allyltoluidine . Before Perkin 's discovery , all dyes and pigments were derived from roots , leaves , insects , or , in the case of Tyrian purple , molluscs .

Quinine wouldn 't be successfully synthesized until 1918 . Synthesis remains elaborate , expensive and low yield , with the additional problem of separation of the stereoisomers . Though quinine is not one of the major drugs used in treatment , modern production still relies on extraction from the cinchona tree .

= = 20th century = =

= = = Etiology : Plasmodium tissue stage and reproduction = = =

Relapses were first noted in 1897 by William S. Thayer , who recounted the experiences of a physician who relapsed 21 months after leaving an endemic area . He proposed the existence of a tissue stage . Relapses were confirmed by Patrick Manson , who allowed infected *Anopheles* mosquitoes to feed on his eldest son . The younger Manson then described a relapse nine months after his apparent cure with quinine .

Also , in 1900 Amico Bignami and Giuseppe Bastianelli found that they could not infect an individual with blood containing only gametocytes . The possibility of the existence of a chronic blood stage infection was proposed by Ronald Ross and David Thompson in 1910 .

The existence of asexually @-@ reproducing avian malaria parasites in cells of the internal organs was first demonstrated by Henrique de Beaurepaire Aragão in 1908 .

Three possible mechanisms of relapse were proposed by Marchoux in 1926 (i) parthenogenesis of macrogametocytes : (ii) persistence of schizonts in small numbers in the blood where immunity inhibits multiplication , but later disappears and / or (iii) reactivation of an encysted body in the

blood . James in 1931 proposed that sporozoites are carried to internal organs , where they enter reticuloendothelial cells and undergo a cycle of development , based on quinine 's lack of activity on them . Huff and Bloom in 1935 demonstrated stages of avian malaria that transpire outside blood cells (exoerythrocytic) . In 1945 Fairley et al. reported that inoculation of blood from a patient with *P. vivax* may fail to induce malaria , although the donor may subsequently exhibit the condition . Sporozoites disappeared from the blood stream within one hour and reappeared eight days later . This suggested the presence of forms that persist in tissues . Using mosquitoes rather than blood , in 1946 Shute described a similar phenomenon and proposed the existence of an ' x @-@ body ' or resting form . The following year Sapero proposed a link between relapse and a tissue stage not yet discovered . Garnham in 1947 described exoerythrocytic schizogony in *Hepatocystis* (*Plasmodium*) *kochi* . In the following year Shortt and Garnham described the liver stages of *P. cynomolgi* in monkeys . In the same year a human volunteer consented to receive a massive dose of infected sporozoites of *P. vivax* and undergo a liver biopsy three months later , thus allowing Shortt et al. to demonstrate the tissue stage . The tissue form of *Plasmodium ovale* was described in 1954 and that of *P. malariae* in 1960 in experimentally infected chimpanzees .

The latent or dormant liver form of the parasite (hypnozoite) , apparently responsible for the relapses characteristic of *P. vivax* and *P. ovale* infections , was first observed in the 1980s . The term hypnozoite was coined by Miles B. Markus while a student . In 1976 , he speculated : " If sporozoites of *Isospora* can behave in this fashion , then those of related Sporozoa , like malaria parasites , may have the ability to survive in the tissues in a similar way . " In 1982 , Krotoski et al reported identification of *P. vivax* hypnozoites in liver cells of infected chimpanzees .

== Malariotherapy ==

In the early twentieth century , before antibiotics , patients with tertiary syphilis were intentionally infected with malaria to induce a fever ; this was called malariotherapy . In 1917 , Julius Wagner @-@ Jauregg , a Viennese psychiatrist , began to treat neurosyphilitics with induced *Plasmodium vivax* malaria . Three or four bouts of fever were enough to kill the temperature @-@ sensitive syphilis bacteria (*Spirochaeta pallida* also known as *Treponema pallidum*) . *P. vivax* infections were terminated by quinine . By accurately controlling the fever with quinine , the effects of both syphilis and malaria could be minimized . While about 15 % of patients died from malaria , this was preferable to the almost @-@ certain death from syphilis . Therapeutic malaria opened up a wide field of chemotherapeutic research and was practised until 1950 . Wagner @-@ Jauregg was awarded the 1927 Nobel Prize in Physiology or Medicine for his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica .

Henry Heimlich has advocated malariotherapy as a treatment for AIDS , and some studies of malariotherapy for HIV infection have been performed in China . The CDC does not recommend the use of malariotherapy for HIV .

== Panama Canal and vector control ==

In 1881 , Dr. Carlos Finlay , a Scottish physician practising in Havana , theorized that yellow fever was transmitted by a specific mosquito , later designated *Aedes aegypti* . The theory remained controversial for twenty years until confirmed in 1901 by Walter Reed . This was the first scientific proof of a disease being transmitted exclusively by an insect vector , and demonstrated that control of such diseases necessarily entailed control or eradication of its insect vector .

Yellow fever and malaria among workers had seriously delayed construction of the Panama Canal . Mosquito control instituted by William C. Gorgas dramatically reduced this problem .

== Antimalarial drugs ==

=== Chloroquine ===

Johann " Hans " Andersag and colleagues synthesized and tested some 12 000 compounds , eventually producing Resochin® as a substitute for quinine in the 1930s . It is chemically related to quinine through the possession of a quinoline nucleus and the dialkylaminoalkylamino side chain . Resochin (7-chloro-4-(diethylamino)-1-methylbutyl amino quinoline) and a similar compound Sontochin (3-methyl Resochin) were synthesized in 1934 . In March 1946 , the drug was officially named Chloroquine . Chloroquine is an inhibitor of hemozoin production through biocrystallization . Quinine and chloroquine affect malarial parasites only at life stages when the parasites are forming hemozoin pigment (hemozoin) as a byproduct of hemoglobin degradation . Chloroquine resistant forms of *P. falciparum* emerged only 19 years later . The first resistant strains were detected around the Cambodia - Thailand border and in Colombia , in the 1950s . In 1989 , chloroquine resistance in *P. vivax* was reported in Papua New Guinea . These resistant strains spread rapidly , producing a large mortality increase , particularly in Africa during the 1990s .

=== Artemisinins ===

Systematic screening of traditional Chinese medical herbs was carried out by Chinese research teams , consisting of hundreds of scientists in the 1960s and 1970s . Qinghaosu , later named artemisinin , was cold extracted in a neutral milieu (pH 7-8) from the dried leaves of *Artemisia annua* .

Artemisinin was isolated by pharmacologist Tu Youyou (Nobel Prize in Physiology or Medicine , 2015) . Tu headed a team tasked by the Chinese government with finding a treatment for chloroquine resistant malaria . Their work was known as Project 523 , named after the date it was announced - 23 May 1967 . The team investigated more than 2000 Chinese herb preparations and by 1971 had made 380 extracts from 200 herbs . An extract from qinghao (*Artemisia annua*) was effective but the results were variable . Tu reviewed the literature , including Zhou hou bei ji fang (A handbook of prescriptions for emergencies) written in 340 BC by Chinese physician Ge Hong . This book contained the only useful reference to the herb : " A handful of qinghao immersed with two litres of water , wring out the juice and drink it all . " Tu 's team subsequently isolated a nontoxic , neutral extract that was 100 % effective against parasitemia in animals . The first successful trials of artemisinin were in 1979 .

Artemisinin is a sesquiterpene lactone containing a peroxide group , which is believed to be essential for its anti-malarial activity . Its derivatives , artesunate and artemether , have been used in clinics since 1987 for the treatment of drug resistant and drug sensitive malaria , especially cerebral malaria . These drugs are characterized by fast action , high efficacy and good tolerance . They kill the asexual forms of *P. berghei* and *P. cynomolgi* and have transmission blocking activity . In 1985 , Zhou Yiqing and his team combined artemether and lumefantrine into a single tablet , which was registered as a medicine in China in 1992 . Later it became known as Coartem . Artemisinin combination treatments (ACTs) are now widely used to treat uncomplicated falciparum malaria , but access to ACTs is still limited in most malaria endemic countries and only a minority of the patients who need artemisinin based combination treatments receive them .

In 2008 White predicted that improved agricultural practices , selection of high yielding hybrids , microbial production , and the development of synthetic peroxides would lower prices .

=== Insecticides ===

Efforts to control the spread of malaria suffered a major setback in 1930 . Entomologist Raymond Corbett Shannon discovered imported disease bearing *Anopheles gambiae* mosquitoes living in Brazil (DNA analysis later revealed the actual species to be *A. arabiensis*) . This species of mosquito is a particularly efficient vector for malaria and is native to Africa . In 1938 , the introduction of this vector caused the greatest epidemic of malaria ever seen in the New World . However ,

complete eradication of *A. gambiae* from northeast Brazil and thus from the New World was achieved in 1940 by the systematic application of the arsenic @-@ containing compound Paris green to breeding places , and of pyrethrum spray @-@ killing to adult resting places .

===== DDT =====

Austrian chemist Othmar Zeidler is credited with the first synthesis of DDT (DichloroDiphenylTrichloroethane) in 1874 . The insecticidal properties of DDT were identified in 1939 by chemist Paul Hermann Müller of Geigy Pharmaceutical . For his discovery of DDT as a contact poison against several arthropods , he was awarded the 1948 Nobel Prize in Physiology or Medicine . In the fall of 1942 , samples of the chemical were acquired by the United States , Britain and Germany . Laboratory tests demonstrated that it was highly effective against many insects .

Rockefeller Foundation studies showed in Mexico that DDT remained effective for six to eight weeks if sprayed on the inside walls and ceilings of houses and other buildings . The first field test in which residual DDT was applied to the interior surfaces of all habitations and outbuildings was carried out in central Italy in the spring of 1944 . The objective was to determine the residual effect of the spray upon Anopheline density in the absence of other control measures . Spraying began in Castel Volturno and , after a few months , in the delta of the Tiber . The unprecedented effectiveness of the chemical was confirmed : the new insecticide was able to eradicate malaria by eradicating mosquitoes . At the end of World War II , a massive malaria control program based on DDT spraying was carried out in Italy . In Sardinia ? the second largest island in the Mediterranean ? between 1946 and 1951 , the Rockefeller Foundation conducted a large @-@ scale experiment to test the feasibility of the strategy of " species eradication " in an endemic malaria vector . Malaria was effectively eliminated in the United States by the use of DDT in the National Malaria Eradication Program (1947 ? 52) . The concept of eradication prevailed in 1955 in the Eighth World Health Assembly : DDT was adopted as a primary tool in the fight against malaria .

In 1953 , the World Health Organization (WHO) launched an antimalarial program in parts of Liberia as a pilot project to determine the feasibility of malaria eradication in tropical Africa . However , these projects encountered difficulties that foreshadowed the general retreat from malaria eradication efforts across tropical Africa by the mid @-@ 1960s .

DDT was banned in the US in 1972 , after the discussion opened in 1962 by Silent Spring , written by American biologist Rachel Carson , which launched the environmental movement in the West . The book catalogued the environmental impacts of indiscriminate DDT spraying and suggested that DDT and other pesticides cause cancer and that their agricultural use was a threat to wildlife . The U.S. Agency for International Development supports indoor DDT spraying as a vital component of malaria control programs and has initiated DDT and other insecticide spraying programs in tropical countries .

===== Pyrethrum =====

Other insecticides are available for mosquito control , as well as physical measures , such as draining the wetland breeding grounds and the provision of better sanitation . Pyrethrum (from the flowering plant *Chrysanthemum* [or *Tanacetum*] *cinerariaefolium*) is an economically important source of natural insecticide . Pyrethrins attack the nervous systems of all insects . A few minutes after application , the insect cannot move or fly , while female mosquitoes are inhibited from biting . The use of pyrethrum in insecticide preparations dates to about 400 BCE . Pyrethrins are biodegradable and break down easily on exposure to light . The majority of the world 's supply of pyrethrin and *Chrysanthemum cinerariaefolium* comes from Kenya . The flower was first introduced into Kenya and the highlands of Eastern Africa during the late 1920s . The flowers of the plant are harvested shortly after blooming ; they are either dried and powdered , or the oils within the flowers are extracted with solvents .

===== Research =====

===== Avian , mouse and monkey models =====

Until the 1950s , screening of anti malarial drugs was carried out on avian malaria . Avian malaria species differ from those that infect humans . The discovery in 1948 of *Plasmodium berghei* in wild rodents in the Congo and later other rodent species that could infect laboratory rats transformed drug development . The short hepatic phase and life cycle of these parasites made them useful as animal models , a status they still retain . *Plasmodium cynomolgi* in rhesus monkeys (*Macaca mulatta*) were used in the 1960s to test drugs active against *P. vivax* .

Growth of the liver stages in animal free systems was achieved in the 1980s when pre erythrocytic *P. berghei* stages were grown in w138 , a human embryonic lung cell line (cells cultured from one specimen) . This was followed by their growth in human hepatoma line HepG2 . Both *P. falciparum* and *P. vivax* have been grown in human liver cells ; partial development of *P. ovale* in human liver cells was achieved ; and *P. malariae* was grown in chimpanzee and monkey liver cells .

The first successful continuous malaria culture was established in 1976 by William Trager and James B. Jensen , which facilitated research into the molecular biology of the parasite and the development of new drugs . By using increasing volumes of culture medium , *P. falciparum* was grown to higher parasitemia levels (above 10 %) .

===== Diagnostics =====

The use of antigen based malaria rapid diagnostic tests (RDTs) emerged in the 1980s . In the twenty first century Giemsa microscopy and RDTs became the two preferred diagnostic techniques . Malaria RDTs do not require special equipment and offer the potential to extend accurate malaria diagnosis to areas lacking microscopy services .

===== A zoonotic malarial parasite =====

Plasmodium knowlesi has been known since the 1930s in Asian macaque monkeys and as experimentally capable of infecting humans . In 1965 a natural human infection was reported in a U.S. soldier returning from the Pahang Jungle of the Malaysian peninsula .