Theodor Bilharz and bilharziasis

(schistosomiasis) – a German contribution to research into tropical diseases.

Dr. med. Lothar Reinbacher

Preface

Germany has a long tradition in the research and treatment of tropical diseases. To begin with, bold explorers, geologists, ethnologists and zoologists penetrated the heart of Africa. They were followed later by doctors from the old world who devoted themselves to the medical care of the indigenous populations. Curiosity drove the Swabian doctor Maximilian Theodor Bilharz (1825–1862) from Sigmaringen to Egypt. He promised to make a name for himself in the world of science by successfully tracking down new discoveries and unknown diseases. For twelve years he worked in Cairo as a pathologist, anatomist, specialist in internal medicine and surgeon. His description of the effector organ of the Nile electric catfish and the discovery of bilharziasis, which was named after him and which 300 million people now suffer from in the world, made him famous. His pioneering work provided the stimulus for others to find drugs to treat tropical diseases. In 1908, with its antileprosy drug Antileprol, Bayer laid the foundations for the unique development of a large number of drugs to treat tropical parasitic diseases. One in four people in the world are affected by these epidemics. However, one must recognise that the control of these is not simply a medical and epidemiological, but primarily a political problem.

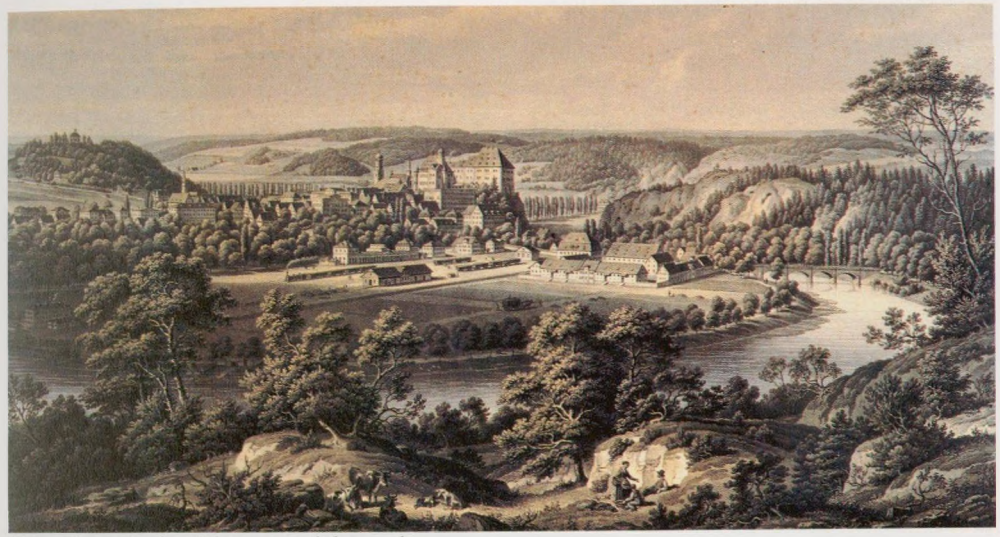
Stages in the life of a researcher

The „house on the corner" in Ahornstrasse, Sigmaringen, Maximilian Theodor Bilharz's birthplace (1825)

The major event in 1850 that steered the then 25-year old Maximilian Theodor Bilharz onto a completely new course was a letter from his tutor at Tübingen, Professor Wilhelm Griesinger. A specialist in internal medicine, he asked whether Bilharz would like to accompany him to Cairo as his assistant.

Court Adviser Joseph Anton Bilharz and his wife Elisa

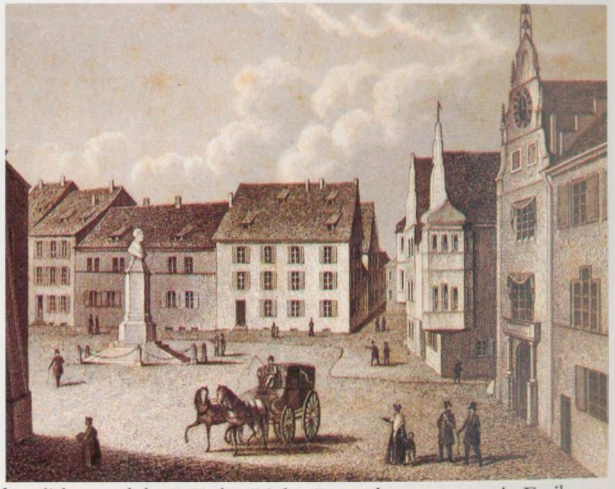
Bilharz agreed gladly and on May 12, 1850, wrote an exultant letter to his parents in Sigmaringen: "What news! I am still trembling with excitement and last night I didn't sleep a wink. All my hopes fulfilled at a stroke! To have it all given to one on a plate. It's simply incredible."
As a student Bilharz had shown he had a gift for thorough, patient research work. The only thing that mattered to him was science – he felt it was his mission in life. In his home town, a sleepy residential place with a population of 1,200 where his father enjoyed considerable respect as a Court Adviser in the service of the Prince of Sigmaringen-Hohenzollern and where he had himself taken his civil service examinations on April 17, 1849, Bilharz was afraid that as a country doctor he would stagnate intellectually.
His father was the first of ten children, came from Herbolzheim in Baden, had studied political sciences at Freiburg and had entered the service of the Prince of Sigmaringen-Hohenzollern in 1817. He was an upright citizen and a caring father. His wife Elisa, who was twelve years his junior, kind-hearted, good-natured and deeply religious, gave him nine children. Their eldest son, Theodor, born on March 23, 1825, was followed by five more sons and three daughters.
At a very early age Theodor had already made his own collection of carefully mounted butterflies, grasshoppers, beetles and dried plants and written a "Guide to Butterfly-Spotting" and a "Catalogue of the Coleoptera found around Sigmaringen". From this time one can still see the six-part, folding lampshade he decorated with herbarium plants and a little box containing 22 glass slides with microscopic specimens, a few of which are still well preserved: they



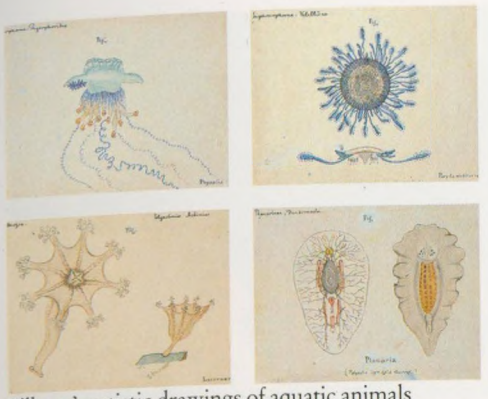
Sigmaringen in the 19th century (lithograph)

show scales from butterfly wings, sections through wood, cork and stems of plants which have survived a century-and-a-half in this way.
At the age of eleven, Theodor surprised his teachers at the Sigmaringen Hedingen Grammar School with a Latin poem on the eruption of Mt. Vesuvius in AD 79. A remarkable characteristic was already emerging in young Theodor Bilharz: he was always faithfully devoted to his teachers and professors. His thirst for knowledge drove him to ask new questions constantly and gave him perseverance and patience – qualities that every researcher needs if he is to reach his goal.
In 1842, Theodor Bilharz spent his school holidays walking through the Black Forest and in 1843 he walked as far as Geneva, Lyon and Lake Lucerne. After taking his school finishing exam (1843), he moved on to Freiburg. He wanted to become a doctor but to do this he first had to study philosophy for two years. At the same time he also attended lectures on archaeology, anthropology, art history, psychology, ethics, German language and literary history. He was never involved in the usual student revels, he avoided student dances,

The Bilharz family's Biedermeier living room

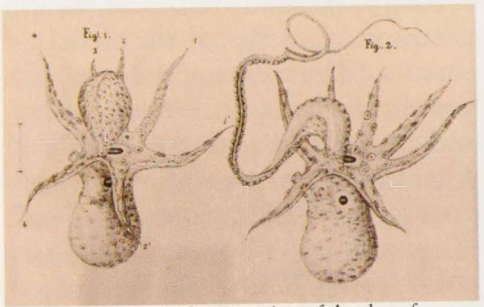


The student Theodor Bilharz at the age of 21 (lithograph by J. Kuh). Right: Rotteck monument in Freiburg

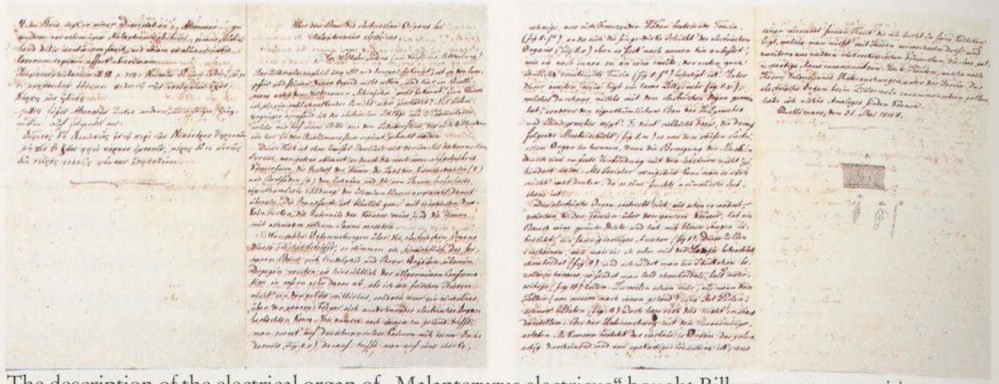


Bilharz's artistic drawings of aquatic animals

"pub crawls" and boastful drinking bouts.
In 1845 as a 20-year old student he moved to Tübingen where he quickly made friends with Griesinger who was then 28 – a friendship which later was to fade rapidly under the physical and emotional stresses and strains of Cairo.
In 1846 Bilharz won a science prize from the Medical Faculty for his treatment of the theme "Blood is a precious fluid". He used the gold medal he was awarded to buy a microscope from Georg Oberhäuser who at the time in Paris was making the best microscopes available. The world of the microcosm, in which he buried himself passionately from then onwards, fascinated Bilharz more than the political upheavals in the student world in 1847 and 1848. But yet he made personal sacrifices in supporting a fellow student from Freiburg – a political fanatic J. M. Hägele who was always in financial trouble and survived some terrible periods of hunger.
Theodor Bilharz studied for seven semesters in Tübingen. After his finals he returned to Freiburg, became a member and almost imme-



Theodor Bilharz had excellent school reports (left). Drawing of the dwarf tapeworm discovered by Bilharz (middle); Argonauta Argo (right)

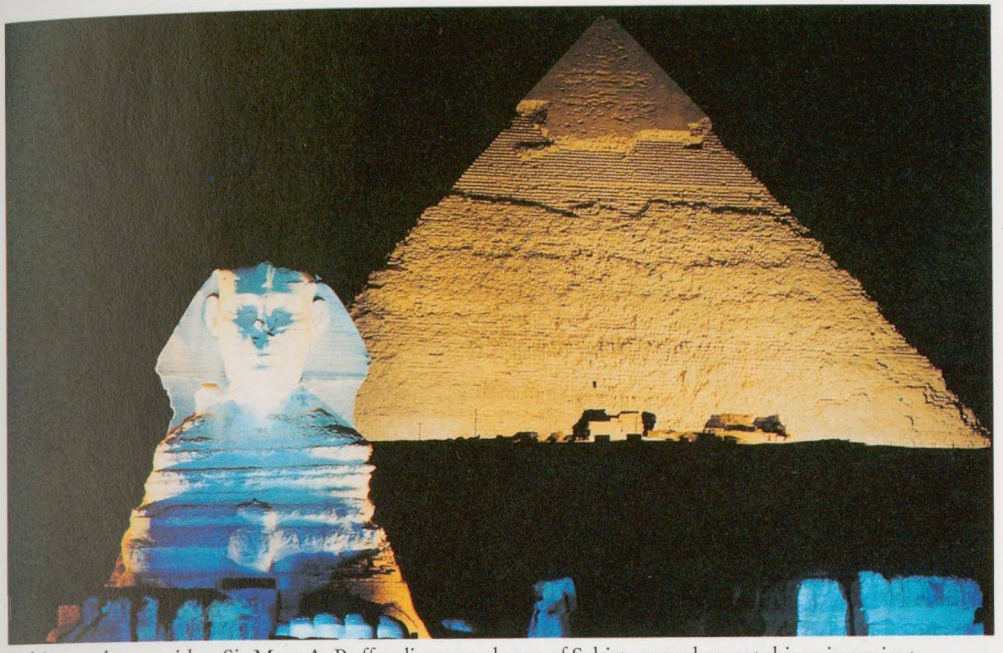


The description of the electrical organ of „Malapterurus electricus“ bought Bilharz great recognition

diately Secretary on the "Society for the Furtherment of Natural Sciences in Freiburg". His passionate dedication, thirst for knowledge and perseverance earnt him the position of "Temporary Vice-Chancellor for one year". As Chief Assistant at the Institute of Pathology and Anatomy he was relieved of his major financial worries and was able to take his brothers and sisters under his wing to take some of the burden off his parents. "That year in Freiburg," he wrote later, "was the most pleasant and the happiest year of my life."
After Griesinger's surprising invitation to Egypt, Bilharz submitted his resignation to his boss, the pathologist Professor Kobelt, the very next day. Three days later he hurried to see his family in Sigmaringen and on May 25, 1850, set off on the journey to farthest Egypt.
As he was saying farewell to his parents and his brothers and sisters, he was already on his way in his mind. The prospect of an exciting life of research in the land of the pharaohs eased the pain of separation somewhat. But did this cheerful traveller realise what risks his stay in a tropical country really entailed? Twelve years to the day after Griesinger's offer arrived – on May 9, 1862, – Theodor Bilharz fell victim to a typhoid infection.

Bilharz's grave in the old part of Cairo

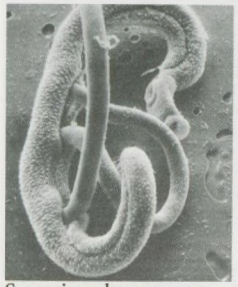
Portrait of a disease



Sphinx and pyramids – Sir Marc A. Ruffer discovered eggs of Schistosoma haematobium in ancient Egyptian mummies

The most obvious symptom of bilharziasis is haematuria to which it owes its original name: dysentery with blood-tinged urine. The detection of eggs excreted in the faeces or urine confirms diagnosis. The shape of the eggs also helps to identfiy what species of schistosoma the parasite is. Bilharziasis is caused by parasitic trematodes which use the blood and lymph vessels of the host as their pathways and live together in pairs. Paired blood flukes can stay in a human for as long as 30 years.
They lodge in the portal system and in the venous plexus of the bladder; the stronger male fluke measuring 6–12 mm curls into a cylinder-like fold, the gynaecophoric canal, in which he clasps the more delicate, slightly longer female. The pair penetrate the smallest veins against the blood flow and it is there that the female starts laying her eggs. Bilharz did not attribute any significance to the different shape of the portal and the bladder wall flukes, which 56 years later were distinguished as Schistosoma mansoni and S. haematobium, but he did produce diagrams of the two different forms.
The female, which consumes about 55,000 erythrocytes an hour as food, releases between 300 and 3000 eggs

into the bloodstream each day. This huge number of eggs is the real problem for the host body because where bunches of eggs get lodged,



Scanning electron micrograph of the paired flukes

Paired flukes in 5-fold magnification

microembolisms, necroses and granulomas develop. However, most of the eggs penetrate the wall of the large intestine (Schistosoma mansoni and S. japonicum) or the walls of the genitourinary tract (Schistosoma

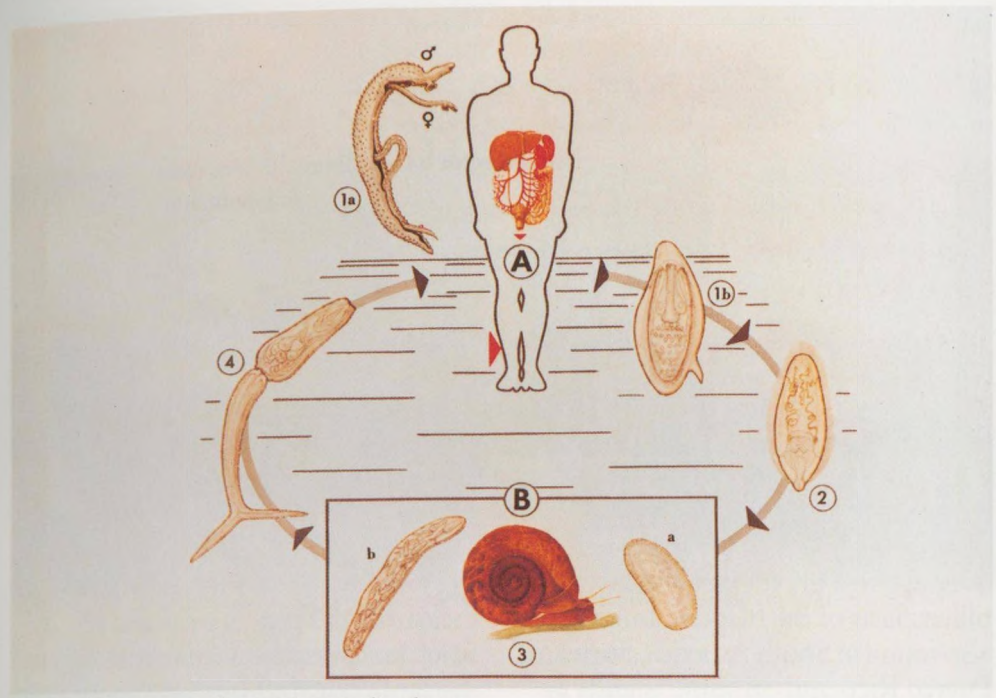
Rural population is informed about bilharziasis

haematobium). Once they have been excreted by the human host, they pass into water courses and irrigation channels.

Miracidia (swimming larvae) emerge from the eggs. Within 48 hours, depending on the type of Schistosoma, they have to find a specific intermediary host snail where they can then transform into sporocysts. Within 20–40 days the sporocysts start to form cercariae. An infected snail can produce hundreds of thousands of cercariae in only a matter of months.
These are approximately 0.5 mm in size and have two large suckers and a forked tail. They swim out of the snail's breathing cavity into open water where they "lie in wait" for a human being to act as their final host. Once the tail has been shed, secreting glands help the cercariae to penetrate the victim's skin in a matter of seconds and gain access to his or her

Hieroglyphic symbol of bilharziasis: a penis

blood vessels. An itchy, papulous eruption ("Kabure itch") sometimes develops at the point where the cercariae entered. More commonly, what may be referred to as

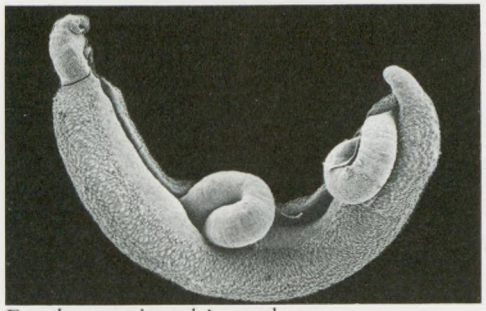


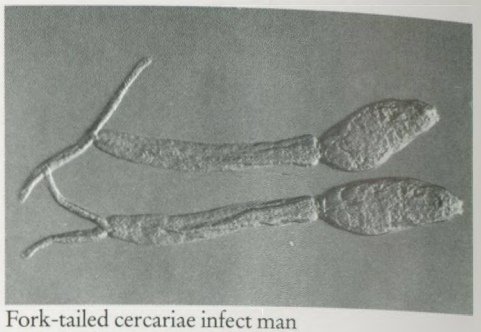
Cycle of infection: snails act as intermediate hosts

Katayama syndrome appears: fever, urticaria, local oedema, inflammation of the liver and spleen and occasionally joint pain.
It is easy to see that people who are in daily contact with irrigation ditches, who have neither tap water nor toilets, are exposed to a constant risk of infection and cannot escape the vicious circle of Schistosoma. Case histories of tourists who have contracted bilharziasis show that just missing one's footing when jumping over a stream is enough to allow cercariae to enter the skin in a split-second.

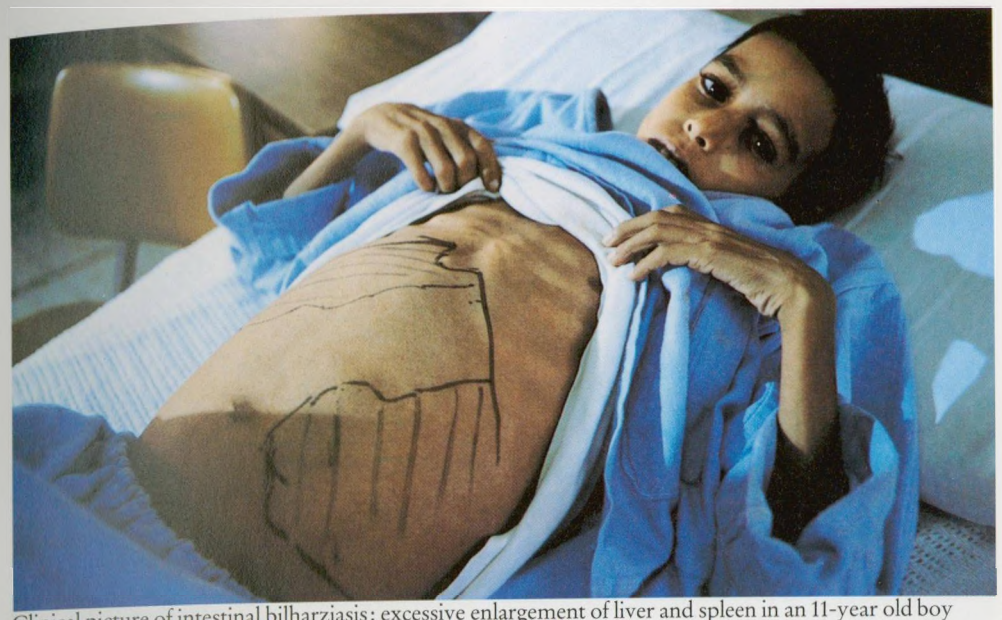
The severity of the symptoms depends not least on the number of flukes that develop and on the site at which they become implanted. A well nourished body can cope with a single fluke pair for a long time, but the central problem in the tropics and subtropics is mass infestation due to constant reinfection.
There are three types of bilharziasis: Bilharziasis of the bladder (caused by Schistosoma haematobium), mainly found in Egypt, the Sudan, Madagaskar, East, West and Southern Africa, leads to haemorrhagic inflammation of the bladder with blood-stained

urine, ureterectasia (distension of the renal duct), bladder papillomas and quite frequently bladder cancer.
The spread of bilharziasis of the gut


Female worm in male's pouch


Fork-tailed cercariae infect man

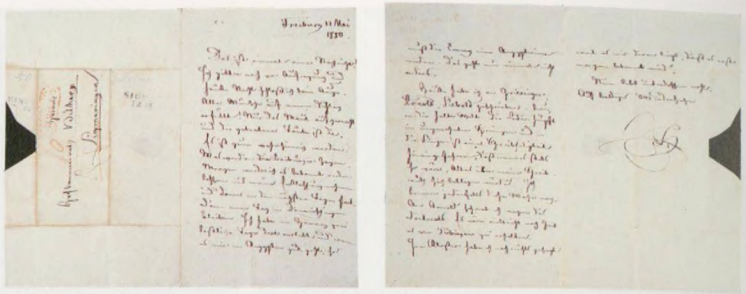
(caused by Schistosoma mansoni) overlaps to a great extent with that of bilharziasis of the bladder, but it is also found in South America, Surinam, Puerto Rico and on some islands in the West Indies. Typical symptoms are mucohaemorrhagic diarrhoea and enlargement of the liver and spleen.
The third type of bilharziasis, (caused by Schistosoma japonicum), affects the digestive tract, especially the liver and spleen. It occurs mainly in mid- and southern China, Japan, Formosa, the Philippines and Sulawesi.
A particular fasture of the East Asiatic species of Schistosoma is that other mammals may be used as the final host as well as humans: such as cattle, water buffalo, mules, donkeys, goats, dogs and pigs.
The different species of schistosomes also favour specific intermediate hosts. The best-known is the brown Biomphalaria glabrata which is the size of a penny; in Tanganyika, Kenya and Uganda one may also find the cornucopia-shaped Bulinus nasutus. The egg from Schistosoma haematobium measures 150 µm, is oval and has a spine at its tip; the S. mansoni egg is the same size, but its spine is not at its tip – it lies at an angle of 45° to the longitudinal axis; the S. japonicum egg is smaller (85 µm), more spherical and has a less noticeable lateral spine.
Parasitoses that have existed for thousands of years and are firmly anchored in the ecological system are impossible to eradicate quickly. Successful use of a vaccine is still a long way off in spite of years of bilharziasis research.
Given that flukes or worms have played a major role since the beginning of mankind, many scientists have even referred to a "perfectly normal" symbiotic relationship. Gerhard Piekarski denies this interpretation: "Symbiosis," according to the parasitologist, "means the coexistence of two different partners to their mutual benefit, whereas parasitism is coexistence with one-sided benefit and exploitation of the host."


Clinical picture of intestinal bilharziasis: excessive enlargement of liver and spleen in an 11-year old boy


Scanning electron micrograph of the paired flukes; the fluke has two suckers


Drawing of the paired flukes

History of a discovery



Theodor Bilharz's letter to his parents, dated May 12, 1850, in which he tells them that he will accompany Griesinger to Cairo

Theodor Bilharz set foot on Egyptian soil on June 18, 1850, in Alexandria and, although his collaboration had not exactly been planned, he was soon employed as assistant to Griesinger who had been appointed abdominal physician, lecturer and head of medicine in Cairo by the Egyptian pasha Abbas I. The two friends shared accommodation in the Ezbekiyeh district of the city. Each day Bilharz would ride the 3.5 km through a park-like residential area to the Kasr-el-Ain Hospital, which lay on the banks of the Nile, opposite Roda Island and a few hundred metres away from the spot where the "Meridien" luxury hotel now stands. As he was trained in anatomy, Bilharz's duty was to perform post mortems on soldiers killed in the Egyptian army. In the cool autopsy room at the hospital he opened up 400 bodies within the first 17 months. "I'm messing about in human entrails," he wrote on April 24, 1851, to his Freiburg lecturer, the famous zoologist Professor Carl Theodor von Siebold (1804–1885), "and have already found four new human intestinal worms..." These were Distomum haematobium (which Bilharz found in every other corpse), Distomum heterophyes (which he only found in a few post mortems), Taenia nana (the small flatworm or cestode) and Pentastomum constrictum. The trematodal researcher often discovered in a single body several hundred specimens of Strongylus duodenalis (Ancylostoma), two to three dozen roundworms and thousands of threadworms.

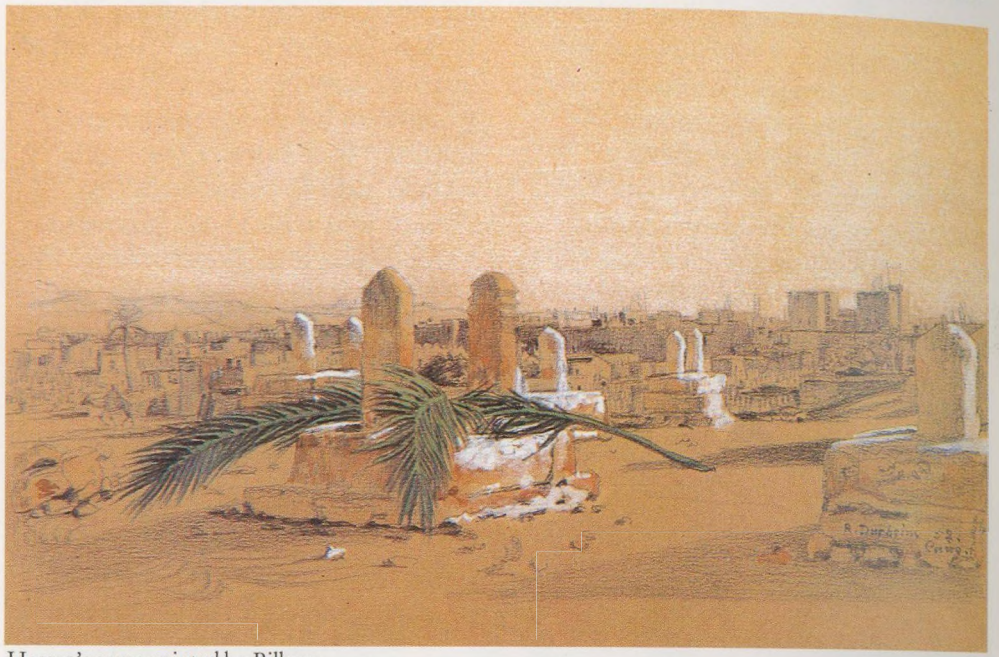
Palace of Soliman Pascha. Here Bilharz died of a typhoid infection on May 9, 1862

Dr. Julius Franz Pascha

Kasr-el-Ain University Hospital where Bilharz worked

Siebold, who published Bilharz's reports in the "Zeitschrift für Wissenschaftliche Zoologie" (Journal of scientific zoology) advised his former student on his choice of nomenclature. "Your portal Distomum," replied Siebold enthusiastically, "which you wish to call Haematobium dispar, is most interesting. The separate species alone are not sufficient justification for establishing a whole new genus... So I would suggest the name Distomum haematobium." – in 1856 Bilharz's friend Heinrich Meckel von Hemsbach changed the generic name Distomum to Bilharzia, but in 1858 the Englishman David F. Weinland made a case for the name Schistosoma haematobium. This name has persisted in Anglo-American literature and in the Third World, although scien-

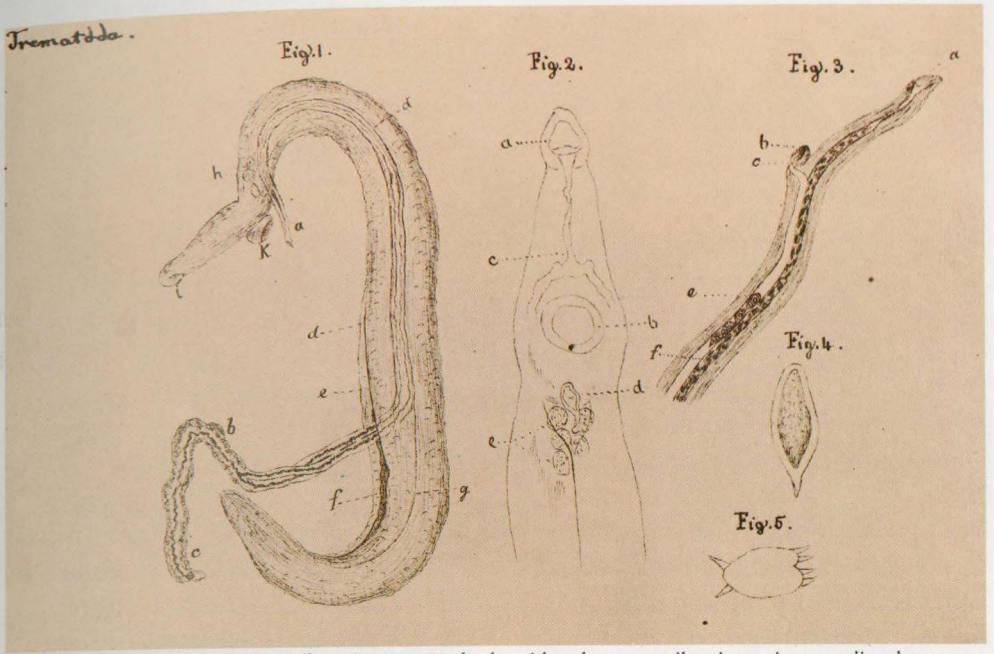
tific preference favours the name Bilharzia.
Theodor Bilharz suspected that the parasite might come "from the water" but he had no idea about the role of the snail. The "intermediary host theory" which caught on later was the object of heated debate for some time until 1914 when the two Japanese researchers Keinosuke Mihairi and Minoru Suzuki identified the Oncomelania snail as the intermediary host of the Bilharzia japonica described by Fujiro Katsurada in 1904. In 1903 Patrick Manson had rightly recognised that the two different shapes of egg produced by the paired flukes must come from two separate species of Distomum. Manson's student Louis W. Sambon therefore ensured that the Bilharzia with the lateral spine became known as Schistosoma mansoni.



Hassan's grave painted by Bilharz

Bilharz in Egypt in 1851

Papyrus Berolinensis Ebers by the Egyptologist and friend of Bilharz Heinrich Brugsch (1827–1894). In the

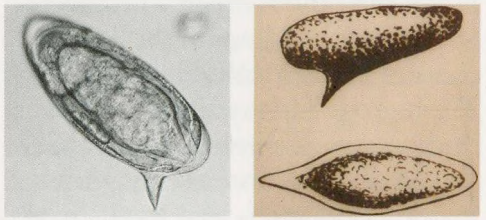


The bisexual worm as seen by Bilharz in 1851. He had no idea about a snail acting as intermediate host

After Bilharz's premature death on May 9, 1862 – at the insistence of Duke Ernst II of Coburg-Gotha, he had joined a hunting party to the Red Sea and became infected there when treating a patient for typhoid fever – his pioneering discovery rapidly fell into oblivion. When in 1875 the Italian doctor Prospero Sonzino at the Kasr-el-Ain Hospital demonstrated once again the existence of paired flukes, this caused something of a sensation – no less of a sensation was the deciphering of the 3,000-year old papyrus ÂÂÂ-disease was described as "an incurable, fatal disease sent by the god of death himself, which torments men and women with severe gut pains, tremblings of the heart, pains of the heart and in the sides." The hieroglyphic symbol for ÂÂÂ-disease is an outstretched penis with drops falling off it – indicating haematuria perhaps?
When in 1910 the bacteriologist and pioneer of palaeopathology, Sir Marc Armand Ruffer (1859–1917), published in the British Medical Journal his

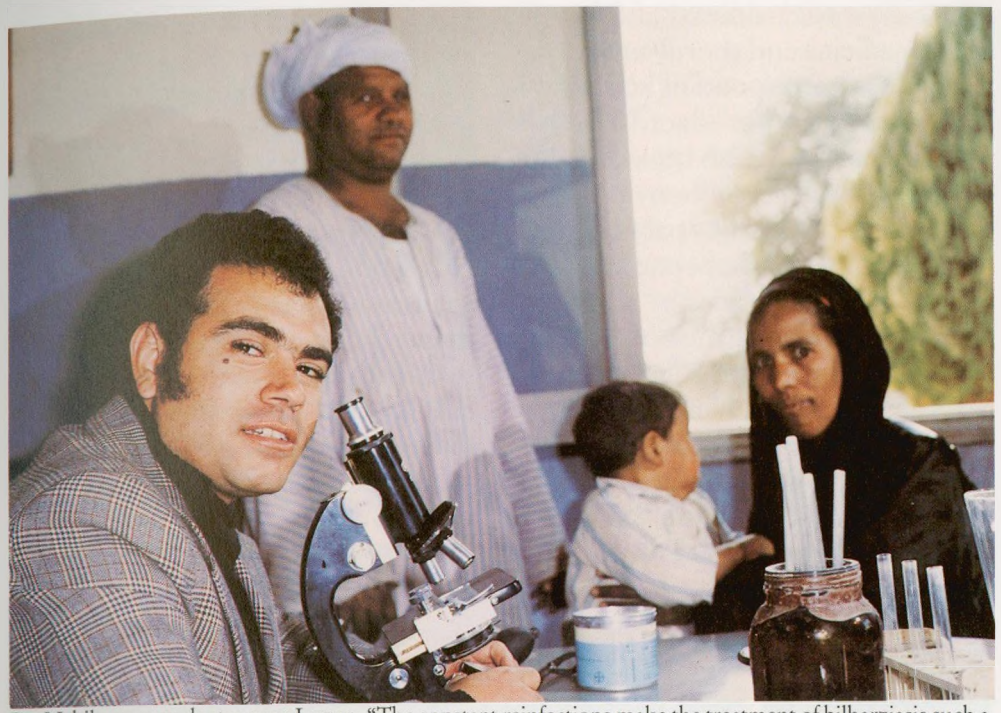
Alfons Bilharz: bilharziasis of the bladder mucosa

discovery of a large number of calcified Bilharzia eggs in the renal tubules of two mummies from the 20th dynasty (1200–1190 B.C.), this proved that the epidemic discovered by Maximilian Theodor Bilharz had already afflicted the Egyptian pharaohs of 3000 years ago. Ruffer's finding was unique because the organs in which paired flukes usually lodge would have been removed before a normal embalming.
However, Ruffer's finding did not remain unique. Clearly identifiable eggs of the paired flukes were also discovered by scientists in other



Egg of Schistosoma mansoni. Left: photo, right: Bilharz's drawing

mummies 4,800 years old.
In 1915 a study commission led by Robert Thomson Leiper finally defined the life-cycle of Bilharzia haematobium and mansoni.
Any report on the activities of Theodor Bilharz must include his four years' work on the electric organ of the electric catfish (Malapterurus electricus Lacepède). Even though his discovery of paired flukes was more significant from the point of view of tropical medicine, his investigations into the electroplaques in the rump of this Nile fish are considered even more important by many zoologists. "I scarcely caught more than two or three fish a month – and never until the afternoons, of course," Bilharz once complained. "The struggle to advance just a tiny step and the Damocles' sword of sunset demanded untiring effort which, due to the heat, the flies and the specimens drying up so quickly,... sometimes turned into a bitter, blind obsession."
Bilharz's grave, which stood unnoticed for decades, lies in the Catholic cemetery in Old Cairo on the Sharia Gabbanet Maslama. His gravestone bears the inscription: "Dr. Theodor Bilharz dedicated his life to the sufferings of mankind, which in 1851 led the way forwards for a cure to the disease which he researched and was named after him. Egypt and Germany remember his life and his work with gratitude and reverence."



Dr. Nabil, country doctor near Luxor: "The constant reinfections make the treatment of bilharziasis such a difficult one".

Three thousand years ago the Egyptians tried to cure ÂÂÂ-disease with pomegranate root, absinth leaves, pistachio seeds, juniper berries, coriander seeds, turpentine, peppermint, red lead and lead vitriol. Hippocrates recommended the same remedies 450 years B. C., as did Galen 200 years A. D. In the orient, these household cures are still recommended today for worms. Based on the experience handed down that antimony helps against intestinal worms, E. R. McDonagh in 1915 and Johann Briand Christopherson in 1918 carried out experiments with intravenous doses of tartar emetic (Tartarus stibiatus) to treat bilharziasis. Because of the poor complex-bonding of trivalent antimony, serious side effects occurred in a number of cases, although the successes aroused the interest of scientists, not just with respect to bilharziasis, but also the different types of leishmaniasis (kala azar, oriental/Delhi/Biskra boil and South American cutaneous leishmaniasis) that responded to treatment with antimony drugs.
In 1925, antimony-pyrocatechol sodium disulphonate potassium (An-

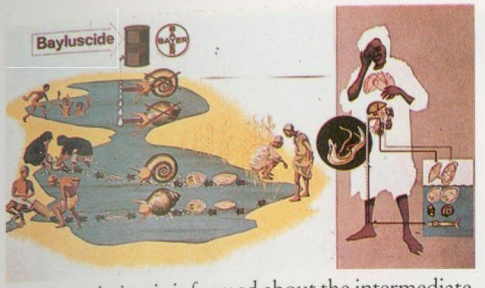
timosan) was introduced into veterinary medicine and shortly after Fouadin, a corresponding sodium compound, was introduced for human therapy. It also belongs to the group of trivalent antimony compounds, but causes less pain on injection than Antimosan because the potassium was replaced by sodium. With the express permission of King Fouad I of Egypt, this effective drug against bilharziasis, lymphogranuloma inguinale, venereal granuloma and cutaneous leishmaniasis was launched by Bayer on 6th September 1929 under the name of Fouadin®.

started experiments to control the plague of snails by adding copper sulphate to rivers and streams. The experiments failed.
There was still no oral form of treatment for bilharziasis. Although Bayer researchers had mastered the cultivation of the intermediate host snails as early as 1932, the experimental infestation of laboratory animals with species of schistosomes that infected humans was still a very difficult procedure. Thousands of substances were tested for their effectiveness against flukes.
In 1943 Professor Walter Kikuth and

The success of any form of anti-schistosomal treatment is determined by the construction of wells and water systems as well as by hygienic conditions

The number of Bilharzia sufferers in Egypt at the time was estimated at between 8 and 9 million. To coincide with this new treatment, Professor Mohammed Khalil Abdel Khalek

his colleague Rudolf Gönnert, working in the Chemotherapy Bayer Laboratory at Elberfeld, stumbled upon a group of highly effective xanthone derivatives (miracils). Miracil-



The population is informed about the intermediate host: Bayluscid poster

D, which was submitted for patent on January 13, 1944, proved to be the best oral anti-schistosomal substance. It was not launched until 1953.
In the mid-sixties another pharmaceutical company also marketed an anti-schistosomal drug. However, similarly to Miracil®-D, its use was associated with adverse effects.
This is why the idea gained ground that tropical parasitic diseases could only really be tackled if the snails were eradicated. After the war Professor Gönnert, as Kikuth's successor, tested over 20,000 compounds against the snail Australorbis glabratus. The most effective substance proved to be N-(2-chloro-4-nitrophenyl1)-5-chloro-salicylamide, which was eventually launched in 1959 as Bayluscid®.
In field studies Bayluscid was clearly superior to other molluscicides: it blocked oxygen intake and carbon dioxide metabolism by the intermediate host. In a standardised trial Bayluscid at a maximum concentration of 0.3 ppm killed the snails and their spawn.
In March 1969, in close cooperation with the Egyptian authorities and with the support of the West German government, Bayer initiated after seven years' preparation a unique field study in the area around the El Fayoum oasis, 100 km south west of Cairo, starting with the first-ever mass treatment of waterways. The area, inhabited by 1.2 million fishermen, craftsmen and farmers and surrounded by desert, has an irrigation system 39,500 km long. The oasis provided ideal conditions because it is only fed

Snails acting as intermediate hosts

by one affluent, the Bahr Yusef, from the Nile. In six separate stages over three years, 600 tonnes of Baylusid were fed into the Bahr Yusef, in order to wipe out all the snails in the 1,790 km² oasis basin.
In spite of enormous organisational difficulties and thanks to a comprehensive follow-up programme for all those who had received medication, all the snails were killed and the incidence among the indigenous population fell from its original 85% to

Schistosoma lodging in a vein

below 17% in 1971.
Children who were born after the snail campaign started remained free of bilharziasis for years.
However, the mass experiment in the El Fayoum region cannot be readily transferred to lakes and rivers in other tropical regions, not even to the Nile and the irrigation systems running from it, because any molluscicide would be swept away by the flow and because the lack of infrastructure in many third world countries presents an insurmountable obstacle to any crossborder project.
Hopes have therefore turned to chemotherapy because in the early 80's Bayer and Merck developed in a joint research project a highly effective substance against all Schistosoma species, namely Biltricide® (praziquantel). A single oral dose of this medication killed the paired flukes lodged in the bloodstream in more than 90% of cases. The claim is that this "lightning cure" should only cost a few D-marks per head and would be successful over a wide area, provided the treatment of large sections of the population could be undertaken in a short time.
Whether or not the innovation Biltricide can actually decimate bilharziasis, largely depends on the governments of the countries concerned and their readiness to cooperate with the World Health Organization (WHO), without whom an effective mass treatment programme is virtually impossible.

The El Fayoum project: workers feeding the molluscicide Bayluscid into the water

The Yahya Hossain family: free from bilharziasis due to proper hygiene and discipline

Tropical research

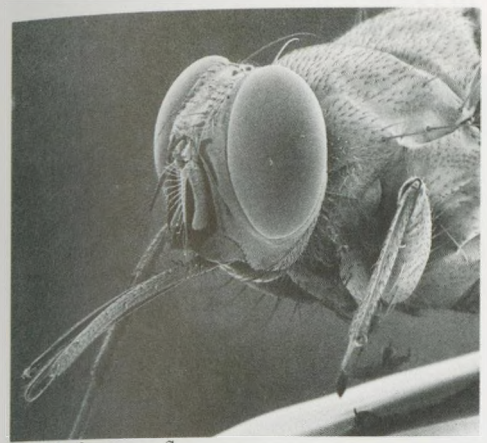
Historical picture: Africans transporting a patient suffering from sleeping sickness

Research in tropical medicine at Bayer is about 80 years old:

Dr. Walter Fischer in Central Africa

the company founded by Friedrich Bayer and Friedrich Weskott on August 1, 1863, which initially manufactured aniline and alizarine dyes, took up production of pharmaceuticals with phenacetin and sulfonal in 1888 and launched its first medication against a tropical disease – the anti-leprosy agent Antileprol.

The stimulus for tropical research had been given by Professor Franz Engel-Bey (1850–1931) who, as an independent student in the 1880's had started in Cairo initial trials with the Indianfolk remedy of chaulmoogra oil. He continued this and in 1905 finally established that leprosy patients fared better with the poorly tolerated oil when it was given in capsule form. The leprosy researcher turned to Bayer where the successful drug Antileprol was synthesised out of the mixture of ethyl esters extracted from the fatty acids contained in chaulmoogra oil.



Head of a tse-tse fly

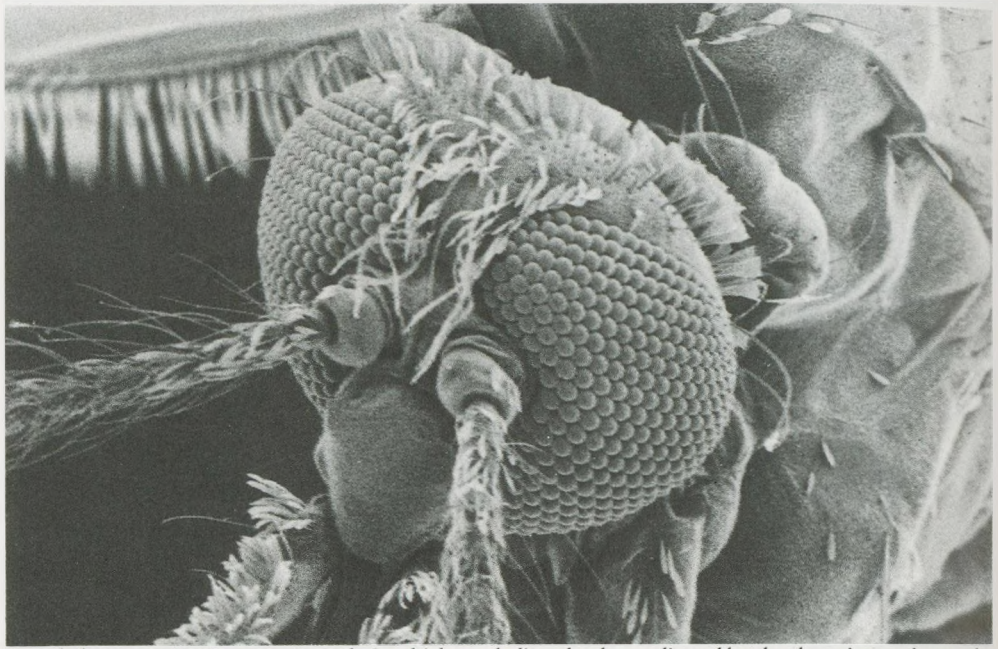
Paul Ehrlich had already turned his attention to the treatment of sleeping sickness which raged in Africa and had first been described in the 14th century by the Arab doctor Al Qualqua Shaidi. In 1911 Ehrlich's former assistant Dr. med. Wilhelm Röhl held the first tests at the Chemotherapy Institute of Bayer. After more than a thousand tests with ureas from the naphthaline series, Röhl found the substances Betrilan and Cetrilan, both effective against trypanosomes. Detrilan, a ureylene from m-amino benzol-m-amino-p-toluyl-l-naphthylamine-4,6,8-trisulphonic acid, proved to be a potent trypanocide. It was given the name Bayer 205. Not until some years later it was found that this substance could also be used against filariasis which affects about 300 million people in Africa, India and South-East Asia.

The first patient to be treated with it was a German who had returned from Fernando Póo. He was given 0.2 g of Bayer 205 i.v. and the same dose again a week later. However, once the patient felt better, he disappeared, never to be seen again.

"A little later," according to Bayer archives, "the first cure was effected on a patient suffering from Trypanosoma rhodesiense, the 36-year old English engineer Christopher Gordon James. In September 1929 he contracted sleeping sickness in the Serengeti district." Doctors at the Liverpool School of Tropical Medicine had already tried in vain to cure him. Then he was treated at the Hamburg Institute of Tropical Medicine: after only 16 hours his fever had subsided and he recovered rapidly. In autumn 1930 Mr. James underwent

Chagas bug feeding on blood

a follow-up examination in Liverpool. The verdict: "He appeared to be in excellent health and claimed he had never felt better in his entire life." Clinical trials on larger numbers of patients met with problems: the usually exhausting three years of work in the heart of Africa which were so successful that in 1923 Germanin could be handed over to the public. In 1955 the number of malaria sufferers in the world was estimated at



Anopheles mosquito. It transmits malaria which was believed to be eradicated but has been increasing again in the recent past

countries in which sleeping sickness was rife were in the hands of former victorious powers. In 1921, however, Bayer management decided to set up an expedition costing 1.5 million D-marks in order to test Bayer 205 (which was to be called "Germanin®" after 1923) in Africa, particularly in the former Belgian Congo and Rhodesia. This developed into an unu-

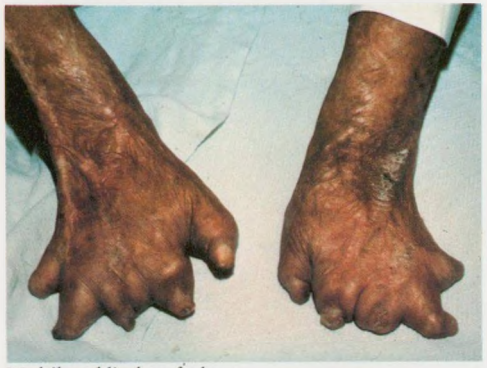
250 million, 2.5 million of whom died each year. The name "mal aria" (bad air) was coined in Italy in the early 17th century. As the result of a tradition the Spaniard Don Juan Lopez de Canizares was cured of malaria (or "intermittent fever") in 1630 by means of Peruvian bark; in 1633 the same successful treatment was reported in Lima. In the mid-18th century experiments began to isolate the active substance from the bark of the Rubiacee Cinchona succiroba. In 1820 the French pharmacists and chemists Pierre-Joseph Pelletier (1788–1842) and Joseph-Bienaimé Caventou (1795–1877) came upon a substance which they called quinine. It was effective against malaria. Not until 60 years later did Charles Louis Alphonse Laveran, a doctor working at the French Military Hospital of Constantine (Algeria) discover microgametes; after a few more years he found schizonts and merozoites. The Italian doctor Camillo Golgi then realised that there must be several species of Plasmodium and his fellow countryman, the zoologist Giovanni Battista Grassi, discovered that only Anopheles mosquitoes transmit malaria to humans.

The fight against malaria brought Bayer tropical research its greatest success. In 1922 Röhl wrote: "Malaria is probably the most important disease on earth. Therein lies one of the greatest challenges of my life". With Plasmochin and Atebrin, which were far superior to quinine, Kikuth and his co-workers achieved a decisive improvement in the treatment of malaria. Atebrin was the first synthetic anti-schizontal agent which was marketed in 1932. After Plasmochin and Atebrin, scientists were able to synthesise the even more effective Resochin®. The simultaneous war against the carrier mosquitoes using DDT strengthened its efficacy. Resochin is still part of standard prophylaxis and treatment

Son of a chief cured of sleeping sickness

of this tropical diesase. The number of malaria sufferers dropped dramatically and many scientists were beginning to predict that this tropical epidemic could finally be eradicated. However, three factors dashed their hopes: malaria mosquitoes developing resistance to DDT, the ban on the use of this most valuable insecticide and an increasing lack of sensitivity among Plasmodia to chloroquine, the active substance of Resochin. In spite of new antimalarials, this tropical epidemic has been greatly on the increase in recent years. Laboratories throughout the world are working on the development of a

malaria vaccine, but it is not yet known when this will become available. So cautious visitors to the tropics still keep well protected under



Multilated limbs of a leper

mosquito nets.
In 1972 another tropical drug emerged from the Research Centre at Wuppertal-Elberfeld: Lampit®, a derivative of nitrofurfurylidene. This promising substance was the first to causally attack Chagas' disease which is raging in Central and South America and which owes its name to the Brazilian Dr. Carlos Chagas who discovered the organism responsible. Leading to years of invalidity or sudden death, caused by Trypanosoma cruzi and transmitted by cone-nosed bugs (Reduviidae) in the night, this "infestation of the poor" had in fact been checked by the Bayer insecticide Baygon®; but there had not been an effective remedy for the causative organism, which lodges in human endothelial and muscle cells first in the lungs, liver, lymph nodes and then in the musculature, multiplies especially in the heart and, in addition, goes through a further development stage in the gut of the Reduviid bugs. Lampit has to be given for a period of 60–120 days which complicates the treatment somewhat. However, for an estimated 7–10 million people infected and another 35 million at a risk of contracting this epidemic, this ist a hope of a cure. Lampit destroys the reproductive development stages of the parasite in the bloodstream and in the body's cells and so broadens the spectrum of potent pharmaceuticals now available against tropical diseases.
Bayer has been engaged in research into schistosomiasis since the thirties. More than 1,000 new chemical compounds p.a. were tested for their effects on bilharziasis.
In the seventies several hundred derivatives were synthesised jointly with E. Merck, Darmstadt. These were to give rise to praziquantel from which the drug Biltricide® was developed.
In extensive trials, some of these made in cooperation with the World Health Organization (WHO), this substance was found to be well tolerated and highly effective. A single dose or one-shot treatment suffices to cure the patients. Biltricide is therefore suited for mass treatment.
Bayer looks back on about 80 years of experience in the field of tropical research. It is this successful research work that accounts for much of the company's high reputation. Contrary to a widely held belief, drugs that produce a cure in at least a high percentage of the cases affected are available for all life-threatening tropical infections today. However, these drugs are by no means used on as large a scale as necessary. The companies still involved in active research in this field of medicine are therefore likely to be more and more discouraged from continuing their research which, as a matter of fact, is very hard to justify from an economical point of view.
Due to the high expenditure of money and technical means on the development of a new drug today, even large pharmaceutical companies engaged in research are no longer able to work in all fields of medicine. They have concentrated their means on a few areas of research.
It has been a long way from Theodor Bilharz's appointment to Cairo to current tropical research. Great success has no doubt been achieved in the combat against tropical diseases; still, the future of tropical research is uncertain in many countries in view of their social and political backgrounds.

Bayer AG
Sektor Pharma
Gesundheitspolitik und Pharma-Information
D-5090 Leverkusen, Bayerwerk

Photography:
Dr. med. Lothar Reinbacher, Kempten (38)
Prof. Dr. rer. nat. Heinz Mehlhorn, Universität Bochum (7)
Prof. Dr. med. Hans Schadewaldt, Universität Düsseldorf (2)
Dr. med. Herbert Lieske, Hamburg (2)
Bayer AG, Leverkusen (11)

Concept and layout:
ABC Presse-Information, Düsseldorf

References:

Dr. med. Angelika Althoff:
Wissenschaftlicher Briefwechsel von und mit Theodor Bilharz
Triltsch Druck und Verlag
Düsseldorf, 1980

Dr. rer. nat. Horst-Bernd Dünschede:
Tropenmedizinische Forschung bei Bayer
Triltsch Druck und Verlag
Düsseldorf, 1971

Gertrud Knabe:
Im Kampf gegen die 11. Plage
Steyler Verlag
Nettetal, 1969

Prof. Dr. med. Hans Schadewaldt,
Institut für Geschichte der Medizin
Universität Düsseldorf
Düsseldorf, 1986
Personal communication

Dr. med. Ernst Senn:
Theodor Bilharz
Schriften des Deutschen Auslands-Instituts Stuttgart
Ausland und Heimat Verlag AG
Stuttgart, 1931

Waltraud Student, Granddaughter of Dr. Alphons Bilharz
Rottweil, 1986
Personal communication

Dipl. rer. pol. Barbara Zwirn,
Great-grandniece of Th. Bilharz
Oberhausen/Pfalz, 1986
Personal communication

E 12-886/841613

Bayer