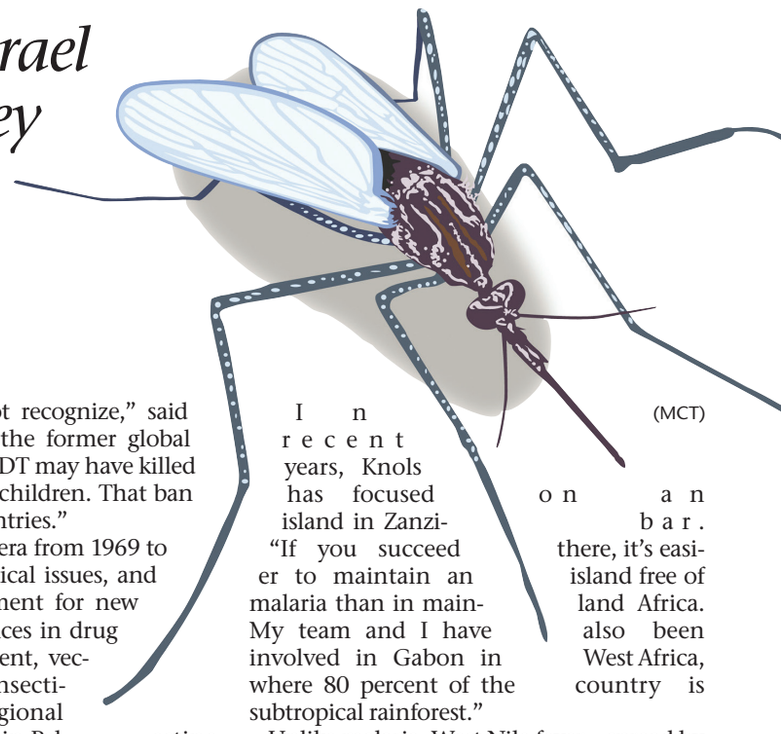
Bed nets won't wipe out a deadly disease

Malaria disappeared from the Jezreel and Hula Valleys when Prof. Israel Kligler devised a holistic approach to eradicating the mosquitoes they carried. The bacteriologist was hailed at a Jerusalem meeting aimed at using the method to help developing countries.

Judy Siegel-Itzkovich reports



(MCT)

Although the Land of Israel in the 1920s and 1930s was considered poor and backward, a now-forgotten Russian-born, American-trained bacteriologist who lived his live out here was a pioneer in wiping out the most important disease in the area – malaria.

Dr. Israel Kligler, who arrived in Mandatory Palestine armed with a doctorate in microbiology in 1920, led the successful effort to eradicate the parasitic disease by draining marshes in the Hula and Jezreel Valleys and spraying larva-infested tracts of land. He was also an expert in yellow fever.

Chief of the bacteriological department of the Hadassah Medical Mission and one of the first professors at the Hebrew University of Jerusalem, he died prematurely at the age of 55 from a heart attack in 1944.

But although few remember him today, what he contributed to practical medical know-how in eliminating malaria can serve as a guiding light to Sub-Saharan Africa, where the majority of cases are, in addition to South America, Asia and other parts of the world, where the disease kills some 660,000 people a year.

Instead of just supplying bed nets to try to keep residents from being bitten at night (but allowing them to remain at risk during the day), Kligler was an activist who advocated fighting the Plasmodium falciparum and other malaria parasites and the Anopheles mosquitoes that carry it, and wiping them out altogether.

Under Kligler's leadership, his Hebrew University department cooperated with US and Allied military authorities in the Middle East in combating epidemic diseases threatening Allied troops. Even the US had malaria until it was wiped out in 1951.

Although malaria was eradicated from this country – thanks to Kligler and his colleagues – more than six decades ago, his doctrine should be emulated to eliminate a disease in which the developed world shows little interest, and whose victims receive little mention. So says Dr. Sanford F. Kuvin, the founder and chairman of the international board of the Hebrew University's Sanford F. Kuvin Center for the Study of Infectious and Tropical Diseases.

Dr. Sanford Kuvin (Courtesy)

Dr. Bart Knols (Courtesy)

Some 100 malaria specialists and graduate students recently attended a five-day meeting in Jerusalem, which was co-hosted by the Kuvin Center and the Hebrew University-Hadassah Braun School of Public Health and Community Medicine.

They came from Israel as well as from Africa, the UK, Europe and the US. Although World Health Organization (WHO) infectious disease officials were invited, they did not attend, except for a retired WHO official. Malaria is considered one of the three most important global infectious diseases, along with tuberculosis and HIV.

The 83-year-old Kuvin, who spends most of his time in Jerusalem after previously being based in Palm Beach, Florida, told *The Jerusalem Post* that malaria was of prime world interest in the early 20th century, but not today – even though it continues to take a major toll on the developing world. There have been three Nobel Prize winners in malaria, but all in the early 1900s -- Ronald Ross in 1902, Camillo Golgi in 1906, and Alphonse Laveran in 1907, Kuvin said.

"British Mandate Palestine was decimated in the 1920's until Dr. Kligler used traditional, time-tested methods to eliminate the Anopheles mosquito that carried the parasite. Now, we are clearly waiting for another Nobel Prize winner for malaria, which has been elusive.

"This is because until recently, there have been few significant advances in malaria eradication and control, despite advances in the use of insecticide-drenched bed nets, water drainage and treatment of swamps and watery areas where the mosquito breeds, the use of new drugs, and early trials of vaccines and advances in molecular biology have brought no dramatic improvement as yet."

Indeed, in 2012, an estimated 219 million cases of malaria were reported and 660,000 people died in 98 countries. "The human species has constantly been subjected to germ warfare by malaria for hundreds of years, but despite our best efforts, the germ warfare of malaria against the human species successfully continues. Furthermore, mosquitoes that carry the malaria parasite know no borders, and now with multiple regional wars and unrest, malaria continues to advance," Kuvin said. Children are the most common victims.

In 1867, Mark Twain wrote in *Innocents Abroad,* while visiting Palestine, that "a desolation is here that not even imagination can grace. We never saw a human being on the whole route."

The people in Israel "have come a long way since Mandatory Palestine," Kuvin continued, "but how to reverse this continuing global trend is clearly what the malaria conference was all about. Not only was it about what I call 'back to the future,' using time-tested techniques that Prof. Israel Kliger and others employed, but improvement has moved forward using a variety of newer techniques."

Kuvin recalled that in 1962, while working at the US National Institutes of Health, "I infected prisoner volunteers by mosquito bite with Plasmosium vivax and Plasmodium cynomolgy bastianelli, a form of monkey malaria,which led to my discovering the first reliable antibody test for malaria. Since this antibody test for malaria was the first for any parasitic infection, I wrote in subsequent publications that followed that a vaccine could not be far behind. But here we are 50 years later, with no effective vaccine which can be routinely used for mass malaria elimination and protection."

In 1955, the WHO submitted to the World Health Assembly of the UN a proposal to eliminate malaria and smallpox within three years. Smallpox elimination was a resounding success, but malaria eradication a dismal failure, the physician said.

Recently, there have been advances in the epidemiology of mosquito elimination, such as that by Kuvin Center scientists like Prof. Yosef Schlein, with an attractive toxic sugar bait to eliminate mosquitos, and recent advances in molecular biology by Prof. Ron Dzikovski, who showed the parasite's ability to express one gene while hiding another 59, because of a unique DNA sequence found in the regulatory regions of the gene family.

"When the reestablishment for global eradication was abandoned in 1969, and death rates from malaria soared, the main reasons for failure were technical challenges which failed to execute time-tested strategies of mosquito elimination, proper insecticide use, and open and safe political borders that the mosquito does not recognize," said Kuvin. "For example, the former global international ban on DDT may have killed as many as 20 million children. That ban still exists in many countries."

African family under bed net (Courtesy)

The post-eradication era from 1969 to 1991 focused on technical issues, and research and development for new tools, leading to advances in drug and vaccine development, vector control and insecticide-treated nets. Regional elimination of malaria in Palestine did not point to global eradication, and that is but one of the reasons for this malaria conference to sort these problems out and go forward.

"Real progress cannot be made without political advocacy as well, led by the US Congress, the US Agency for International Development, the European Union, the Bill and Melinda Gates Foundation, the Global Fund to Fight AIDS, Tuberculosis and Malaria and other major fund-giving bodies," concluded Kuvin. "HIV/AIDS activism made a huge impact in the fight against AIDS. That same financial and political activism must be employed against malaria, which has killed and continues to kill so many millions, mainly children."

ONE OF the other participants in the medical meeting was Dr. Bart Knols, a medical entynologist (insect expert), vector biologist and chairman of the advisory board of the Dutch Malaria Foundation.

He recalled that malaria was wiped out in his country in 1959. "There are not many left in the Netherlands who are working on it. Those who do focus on the situation in Africa and try to help."

He himself has caught malaria nine times, when he lived with his wife for 11 years in Kenya and Tanzania. "My wife almost died of it," he said, noting that it can happen even when using bed nets and taking prophylactic drugs. "You can get bitten during the day as well, but sometimes you catch a strain of parasites that are resistant to the drugs," Knols said. "I was seriously ill for a week, and then it took a week to recover. Our daughter lived as a child for a few years in Kenya; it was fortunate she never got it."

The classic symptom of malaria is a cyclical occurrence of sudden coldness, followed by shivering and then fever and sweating – occurring every two or three days.

"As an entymologist, I try to make their lives miserable. Dr. Kuvin has the right idea of looking 'back to the future.' Malaria was eliminated by Dr. Kligler! About 100 countries that used to suffer from malaria have wiped it out as well. There has to be an integrated approach, because there is no such thing as one magic bullet. One has to diagnose patients properly, take care of them and make an all-out attack on mosquitoes so they don't reach people," declared Knols.

"One must get to the place where mosquitoes are breeding, as in standing water, including marshes. Dr. Kligler understood it was a package deal, and it disappeared here altogether. Malaria in those days was as bad – if not worse – as it is in Africa today. But it's a big job to persuade society, politicians and funding organizations that these old techniques can still be feasible. Handing out free bed nets is easy – but it is only control, not elimination. The UN's approach is insufficient and will only reduce the number of deaths, not elimate them."

In recent years, Knols has focused on an island in Zanzibar. "If you succeed there, it's easier to maintain an island free of malaria than in mainland Africa. My team and I have also been involved in Gabon in West Africa, where 80 percent of the country is subtropical rainforest."

Unlike malaria, West Nile fever – spread by mosquitoes – is caused by a virus, not a parasite. There is a reservoir in nature of this virus. Malaria parasites are found only in mosquitoes or in humans; if you treat people with drugs, it's relatively easy to eliminate malaria. One billion people live in places where the disease has been eliminated. Indeed, Knols noted that "if the Netherlands were again infested, "we would not be happy just handing out bed nets, but this is what still happens in Africa."

The Gates Foundation has, since 2000, spent $2 billion on malaria research – especially on a malaria vaccine. In 2015 it may hit the market, said Knols, "but it would give only partial protection. Like with the flu and HIV, the malaria parasite enemy is constantly changing, and the immune system has to recognize each new form, so it's hard and very expensive to develop an effective vaccine. The strain in Ethiopia is not necessarily the same as that in Senegal or Boswana."

Another problem is that "in the old days, governments could demand that homeowners allow public health people to get into backyards to kill mosquitoes. Today, there are laws that regard this as trespassing."

It would cost billions of dollars to eliminate malaria around the world. "But I can't eliminate it just in the eastern Congo because the country is not safe, there are not enough roads and infrastructure, and it's plagued by rape, civil unrest and war. Some governments have given it priority, but others haven't," said the Dutch scientist.

His lab is working on biological control of malaria. "Mosquitoes are becoming more resistant to insecticides, so we are trying to develop a fungus that is specific for killing the insects. It's a comopolitan type of fungus, and found even in Israel's soil. It works.

"The good news is that several companies are producing this fungus on large scale, for control of pests in agriculture. I will be able to order fungal spores to infect mosquitoes in Tanzania, and they won't be able to bite people."

But Knols added that the insecticide lobby "is out there, and it opposes biological control. They regard us as green dreamers or hippies. Yet it could be done. We are now trying the fungus out at 1,600 Tanzanian homes; it could become mainstream.

"After our Jerusalem meeting, we will support people there and in Gabon, to work with health ministries to eliminate malaria. Those who attended are working on a formal declaration for governments all over the world and the WHO to do better."

He concluded that "we in the developed world have a moral obligation to invest there what we do in developed countries. It brings about clear economic, not to say humane, benefits. There isn't a single child who has to die of malaria, but it has become a forgotten disease.

"Just during our conversation, 10 or 15 African kids have died of malaria."

Fighting anti-Israel boycotts

The science ministers of Israel and Britain have agreed to increase their budget for scientific cooperation and the fight against boycotts against Israel by universities in that country.

Sir David Willetts of Britain and Israel's Science, Technology and Space Minister Yaakov Peri recently reached the understanding in London, where Peri also met with Prime Minister David Camaron and addressed the House of Lords. The cooperation is part of the binational BIRAX program.

The Israeli minister called on the British government to bring an end to the "provocations against Israel" being made by academic organizations in that country. "Israeli science is our pride, but don't let provocations run the scientific cooperation that we have with Britain," Peri advised. "Our cooperation agreement is the most suitable reaction to the calls in Britain to boycott Israel of its researchers and products. Israeli scientists studying and conducting research in Britain have found their environments turned into political rather than academic. This must be stopped," Peri concluded.

ZINC STARVES PATHOGENS

Australian researchers have found that the mineral zinc can starve one of the world's most deadly bacteria by preventing its uptake of an essential metal. The finding, by infectious disease researchers at the University of Adelaide and the University of Queensland, opens the way for further work to design antibacterial agents in the fight against Streptococcus pneumoniae.

This bacterium is responsible for more than a million deaths a year, killing children, the elderly and other vulnerable people by causing pneumonia, meningitis and other serious infectious diseases. Published recently in the journal Nature Chemical Biology, the researchers describe how zinc "jams shut" a protein transporter in the bacteria so that it cannot take up manganese, an essential metal that Streptococcus pneumoniae needs to be able to invade and cause disease in humans.

"It's long been known that zinc plays an important role in the body's ability to protect against bacterial infection, but this is the first time anyone has been able to show how zinc actually blocks an essential pathway causing the bacteria to starve," says project leader Dr. Christopher McDevitt, an infectious diseases expert at the University of Adelaide.

"This work spans fields from chemistry and biochemistry to microbiology and immunology to see, at an atomic level of detail, how this transport protein is responsible for keeping the bacteria alive by scavenging one essential metal (manganese), but at the same time also makes the bacteria vulnerable to being killed by another metal (zinc)," says structural biology Prof. Bostjan Kobe at the University of Queensland. "Without manganese, these bacteria can easily be cleared by the immune system," says Dr McDevitt. "For the first time, we understand how these types of transporters function. With this new information we can start to design the next generation of antibacterial agents to target and block these essential transporters."

NEW WORLDS

• By JUDY SIEGEL-ITZKOVICH

CHROMOSOMES SHOW OFF THEIR SHAPES

Chromosomes – the 46 tightly-wrapped packages of genetic material in our cells – have in the last six decades been depicted as X-shaped formations. But in fact, those neat X's appear only when a cell is about to divide and the entire contents of its genome duplicated. Until now, researchers have not been able to get a good picture of the way that our DNA – some two meters of strands all told – is neatly bundled into the nucleus while enabling day-to-day (non-dividing) gene activity.

A combination of new techniques for sequencing DNA in individual chromosomes and analyzing data from thousands of measurements has given us a new picture of the 3-D structures of chromosomes. This method, the result of an international collaboration, which was recently reported in Nature, promises to help researchers understand the basic processes by which gene expression is regulated and genome stability maintained.

Dr. Amos Tanay of the Weizmann Institute's computer science and applied mathematics and the biological regulation departments develops advanced computer algorithms for analyzing genomic datasets, which can run to billions of bits of information. He and his team, including doctoral students Yaniv Lubling and Eitan Yaffe, joined forces with Dr. Peter Fraser of the UK'sBabraham Institute to try to resolve chromosomal architectures at an unprecedentedly high resolution.

Instead of traditional microscopy techniques, they used the power of modern high-throughput DNA sequencing and developed a sophisticated sequencing method for taking thousands of measurements of the contacts between genes inside single cells. While these techniques vastly improve upon approaches that average the conformations of millions of chromosomes, the data generated from just the few trillionths of a gram of DNA present within a single cell can only be interpreted by advanced statistical methods.

Tanay and his team performed the complex computer analysis that turned millions of DNA sequences into reliable maps describing contacts between genes along individual chromosomes. Using these maps, the scientists were able to produce 3-D models of individual chromosome structures.

Interestingly, the new high resolution depictions of chromosomal architecture indicate that the structure of the same DNA molecule can vary markedly between different cells. At the same time, the results point to some basic principles that underlie the genes' organization. Their arrangement appears to be modular and based on the functions of the thousands of genes embedded within each chromosome. The data suggests that chromosomes expose the more active genes at their boundaries, possibly allowing these genes better access to the cellular machinery that regulates them.

Besides giving us a unique, surprising view of the structure of the chromosomes in our cells, the researchers believe that their method may help uncover the variations in genetic activity between different types of cells.