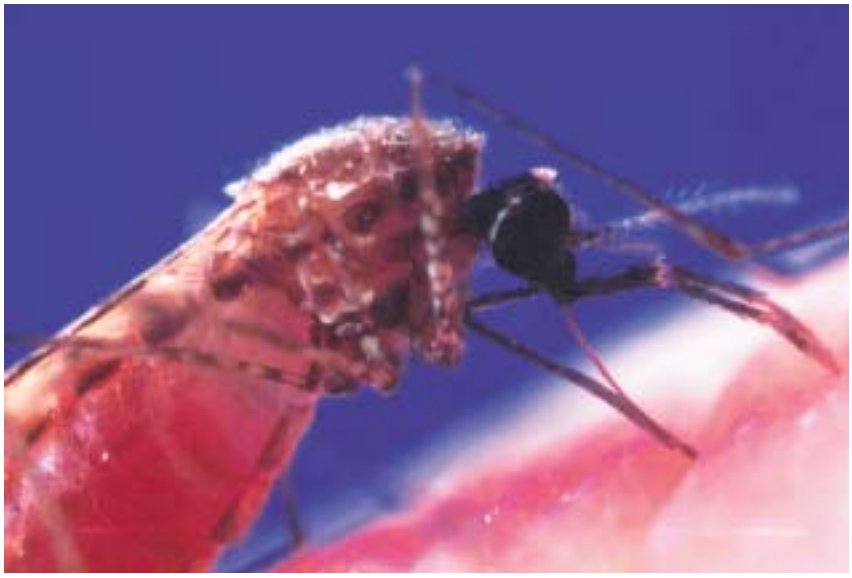
News

Malaria and mosquito genomes sequenced, but funding falls short



WHO/TDR/Stammers

Anopheles gambiae: adult female feeding on human blood.

The genetic code of the complete genomes of *Plasmodium falciparum*, the most lethal of the several malaria parasites, and its major African carrier, the mosquito *Anopheles gambiae*, were published in *Nature* and *Science* this October, bringing these tiny organisms into the same exalted domain as the human genome itself.

Already it turns out that 550 of *P. falciparum*'s 5300 genes are closely related to plant genes — opening the way to research on new drugs based on insecticides. The genes code for — or create — a recently discovered organelle in the body of the parasite called an apicoplast. The apicoplast in turn is very similar to the chloroplast in plant cells, the body that allows plants to photosynthesize, or grow in sunlight.

This doesn't mean that malaria parasites, which are animals, can grow in sunlight. It just means that during their evolution one of them must have absorbed the chloroplast, probably from an alga, found it useful for other purposes, and grew faster and outcompeted their colleagues, creating the *P. falciparum* we know today. The modern organism uses the apicoplast to make fatty acids, similar to cholesterol in humans, that are essential to its survival.

From the early genome data three years ago, a German group identified a particular mechanism in the apicoplast that looked ripe for attack (*Science* 1999; 285:1573-6), and recommended trying an existing drug called fosmidomycin, which had been developed for urinary infections; the group showed it cured mice of malaria, and is now in late clinical trial.

This was one of the first fruits of genome mapping, and represents just one kind of knowledge it can give us: comparative genomics, which entails comparing the letters and organization of the genome of one species with those of another. It may prove useful in accelerating research towards new treatments.

Similar stories are already emerging from *Anopheles gambiae*, the key mosquito vector of malaria. Its gene sequences are being compared with those of the famous laboratory fruitfly, *Drosophila melanogaster,* which itself has been exhaustively researched for several decades. Now it seems we can identify, by comparison and contrast with *Drosophila*, the genes in the mosquito which are responsible for the malaria parasite's survival in the mosquito gut, as well as genes for moulting, reproduction, and successful blood feeding. All these could form new points of attack on the mosquito.

Knowledge of these genomes and the human genome — the parasite, the vector, and its victim — gives us "the opportunity to take a holistic approach in understanding how the parasite interacts with the human host", Alan Cowman, a molecular parasitologist at the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, told *Science*.

Nevertheless the function of two-thirds of the parasite's genes are still mysterious, and perhaps peculiar to the parasite itself. No amount of comparison may determine the function of the proteins they create, and lengthy and difficult research may be required to follow exactly what they do.

It is rather as if, like Galileo, we had turned a telescope for the first time on the Moon, and seen the wonder and detail of its craters and mountains, casting shadows in the sunlight. Suddenly Galileo could compare the Moon with the Earth, yet it was 300 years before anyone landed on Earth's partner in space. So with the genomes of malaria and its vector; we can wonder immediately at the detail of our vision, but it may take a long time and much funding before any of this knowledge turns into a tangible product in the village or the local hospital.

Meanwhile there is competition for limited funding between those who focus on amplifying control with existing tools, such as insecticide-impregnated bednets and education, and those who point to increasing resistance to cheap drugs and insecticides and advocate research for new weapons against the disease and its mosquito vector. For example, on the one hand we have the Roll Back Malaria initiative (RBM), founded in 1998 by WHO, the UN Development Programme (UNDP), the UN Children's Fund (UNICEF) and the World Bank with the goal of halving the world's malaria burden by 2010, which hardly gives time to wait for research. On the other there are bodies like the UNDP, World Bank and WHO Special Programme

WHO/TDR/Mark Edwards

A Yanomami mother with her child who has cerebral malaria. They are at the Centro Amazonico para Investigación y Control de Enfermedades Tropicales clinic, near Puerto Ayacucho, Venezuela.

Malaria takes its constant toll – a postcard from Kenya

In a congested ward in Kisii in the western highlands of Kenya, 50-year-old Nelly Kwamboka wails, curses and collapses in anguish at the foot of the bed. Her young son has just died.

Two months ago, Kisii bore the brunt of an epidemic of highland malaria, which resulted in hundreds of deaths. Nelly is too shocked to walk. She looks pale and exhausted, after trekking many kilometres with her child to reach the hospital.

Nearby, a mother of two, Elizabeth Momanyi from the village of Bomorenda, Suneka, has already lost one son — and her husband — to the epidemic. She rarely seeks medical services for herself, but when her own fever worsened, neighbours intervened, urging her to go to the hospital. But she is not impressed with the treatment she received: ''Attendants at this hospital are cruel,'' she said. ''During the few occasions I have been here, I have had my prescription written before I even described my condition or had any medical examination.''

In a bed close by, Elizabeth Kemunto had been ailing for two months but could not get to the hospital. Instead, she lay waiting for divine intervention. ''We took her to the local pastor for prayers after which she felt better, but then her condition worsened'' says her mother, Eunice Nyamato. But even then, she did not see the doctor, opting to buy over-the-counter drugs.

Kisii residents told the *Bulletin* that they normally use chloroquine as the first line of treatment because it is cheap. But the malaria parasite here is resistant to chloroquine, and to next-line drugs like Fansidar. By the time some neighbours took Elizabeth to hospital, her condition had deteriorated seriously. She may not live.

Even in the capital, Nairobi, malaria takes its toll. In the city's Kibera slums, Stella Wangui, a casual worker at the Nairobi City Council, recalls how she lost her daughter, Angela Muthini, four years ago to the disease. Stella had travelled to her rural home in Embu with her daughter and remembers Angela playing with other children by a nearby stream.

''She probably died because she was playing there — hundreds of mosquitoes were buzzing around the water,'' she said. ''My beautiful little girl died so quickly. Some days later, I became ill too.'' Back in Nairobi she had bouts of fever at regular intervals, but her temperature always returned to normal without medication. She thought that her body was merely reacting to the death of her daughter. But she decided to take medical tests, which revealed that hers was mild form of malaria ''I thought it would kill me the way it did to Angela,'' she said.

According to Kenya's National Malaria Strategy Paper 2001-2010, malaria kills 26 000 children per year in the country and accounts for 30% of all outpatient attendance. ■

James Njoroge, *Nairobi*

for Research on Tropical Diseases (TDR) and public–private partnerships such as the Medicines for Malaria Venture (MMV) and the Malaria Vaccine Initiative (MVI) whose task is to find new tools.

With over a million children and pregnant women dying from malaria in Africa alone each year (see Box), clearly both approaches are necessary. But while the WHO Commission on Macroeconomics and Health estimated that US$ 2.7 billion a year was needed just to control the disease, only about US$ 200 million a year is being spent on it. Roll Back Malaria, which helps countries develop their own programmes and funding sources, has recently been advised by an external commission to focus its efforts on just a handful of African countries. In research MMV has several products in line but just US$ 15 million a year to spend on them, MVI also, with several candidates, has some US$ 50 million, and TDR around US$ 25 million for malaria. Meanwhile pharmaceutical companies estimate that it costs US$ 500 million to discover, develop and market a new product. In total, investment in control and research is about a tenth of the real need.

The malaria and mosquito genomes bring welcome new hope, but having only a tenth of the resources needed weighs heavily. This seems to be the extent of the world's concern for tropical diseases: it is the same ratio by which the Global Fund to Fight AIDS, Tuberculosis and Malaria falls short of the estimated global needs for HIV/AIDS treatment and control (*Bulletin of the World Health Organization* 2002;80:338). ■

Robert Walgate, Bulletin

Argentina's health system devastated but health workers rally

The financial crisis of the past year has had a devastating impact on health care in Argentina.

With an unemployment rate of about 20% and an estimated 19 million of the population of 37 million living below the national poverty line, public clinics and hospitals have been swamped with patients who can no longer participate in private insurance systems sponsored by unions and employers.

Speakers at the Fifth Argentine Health Congress, held in August in Mendoza, painted a stark picture. An estimated 18 million Argentines now have no medical coverage and must depend on the overburdened public health system.

The Argentine peso had been on a par with the US dollar for a decade but with the devaluation it is now worth little more than 25 US cents. This has caused the price of imported drugs and medical supplies to skyrocket and supplies to fall.

"Practically 80% of the supplies we use are imported, from a simple glove to the latest antibiotics," Francisco Díaz, president of the Association of Private Clinics Sanatoriums and Hospitals, told the newspaper *La Nación*.

Rubén Torres, director of Health Services in the Health Ministry, announced that annual per capita spending on health care in Argentina had dropped from US$ 650 to US$ 184 because of the devaluation, a drop from one of the highest rates in Latin America to one of the lowest.

Dr Horacio Mingrone of the F.J. Muñiz Hospital in Buenos Aires said in an interview that patients are waiting longer to seek medical treatment because of their economic situation. "Their first priority is to find a way to live, to eat, the care for their families," he said. "Health comes second."

Dr Mingrone, whose hospital specializes in infectious and respiratory diseases, said that the patients who come to the hospital now are sicker than they were in the past. For example, 40% of the HIV-positive patients he sees for the first time already have AIDS. He added that patients who could have been managed as outpatients with highly active retroviral therapy (HAART) if they had gone to a doctor earlier, now often are admitted with opportunistic infections, such as hepatitis C and lung diseases.

He also noted that doctors in the Buenos Aires province and the capital itself are seeing more cases of diseases associated with poverty and poor hygienic conditions, such as hantavirus and leptospirosis, which formerly occurred primarily in areas outside the capital region.

People suffering from chronic illnesses such as diabetes and AIDS have had great difficulty obtaining the imported drugs they need to maintain their health. In May, the Argentine Society of Nephrology said medical care of the approximately 17 000 Argentines with chronic kidney disease was seriously compromised because of the increase in costs for dialysis supplies.

Recipients of transplanted organs have reported that it has become much more difficult to obtain the immunosuppressant drugs they need to prevent their bodies from rejecting the new organs. And new transplant surgery is often postponed.

Other types of non-emergency surgery have been postponed as well. The construction workers' union insurance plan put 20 pacemaker operations on hold in May. In April, the newspaper *Clarín* reported that Posadas National Hospital in Buenos Aires province had to suspend scheduled operations.

In several provinces, an increase in low-weight births has been reported, an indication that the mothers were undernourished. In Mar de Plata, 13% of the babies born in public hospitals in 2001 weighed less than 2.5 kilos, La Nación newspaper reported in July. It quoted Dr. Liliana Racciati, an obstetrician in charge of the high-risk ward at the Inter-zonal Specialized Maternal-Child Hospital there, as predicting that the percentage would be higher this year.

And psychiatrists in Buenos Aires told Inter Press Services of an increase in the number of people seeking psychiatric help because of stress related to unemployment and an inability to support their families. The number of calls to suicide hotlines has also increased, the news service reported.

Juan Pedro Sapene, a psychiatrist in Santa Fe, told the newspaper *El Litoral* that he was seeing more patients suffering from depression than before. "We see the impact of the crisis on people's emotional and family lives ... Many couples begin to have problems blaming each other for things that in reality have other causes," he said.

The elderly are particularly hard hit. A government social security system, called PAMI insures 3.5 million Argentines, of whom 2.4 million are over 65. The system has been plagued by mismanagement and overspending and is deeply in debt to its suppliers. According to the Pan American Health Organization, the lack of influenza vaccine alone could cause 850 to 4200 deaths among people over 65.

Experts in diagnostic imaging — and improvization

Gabrielle Lofthouse is a half-Argentine fifth year medical student at Guy's, King's and St Thomas's School of Medicine, Kings College, London. She was shocked by the summer she spent this year, after the economic collapse, at the Department of Endocrinological Medicine in a major hospital in Buenos Aires. She told the *Bulletin:*

The greatest contrast is between the very basic facilities that the doctors here are forced to work with and their very high level of clinical knowledge.

Doctors here have no easy access to hi-tech imaging or diagnostic methods, and due to the very weak peso they can no longer afford to maintain what equipment they do have, as it is mostly imported. So they have been forced back upon basic clinical history and examination techniques — and they are quickly becoming extremely skilful at it.

I too had to become an expert, in the matter of the 'Obra Social', the health insurance system of Argentina, which is extremely important in determining what treatment each patient is entitled to receive.

Argentinians, if they are lucky, are members of a health insurance scheme or 'Obra Social' supported by their employers; for example there is an Obra Social for teachers, another for government employees etc. But membership relies on personal contributions to the scheme, and due to the severe economic problems here at the moment, many people are no longer able to pay their membership and so no longer have health cover.

This results in patients being unable to pay for adequate diagnostic methods or treatments. This is a very frustrating situation for both patients and doctors. For example, all drugs here, including generics, are charged at different amounts depending on their quality. So now some patients are unable to pay for the proper prescribed drug — so they buy a poorer quality version which will not have the same effect or may even be detrimental to their health.

I was also shocked, when I was observing biopsies of the thyroid gland, to discover that patients here are now required to buy their own needles and syringes to bring to the hospital to be used for this procedure. One lady was unable to afford all the necessary equipment and as a result was unable to have the procedure. This to me is in such marked contrast to my experience as a student in London, where equipment such as syringes and needles are considered to be throw-away items and are used in large quantities without a second thought being given to whether supplies will run out or not.

Gabrielle Lofthouse was interviewed by Robert Walgate, *Bulletin.*

In February, Health Minister Ginés González García declared a national health emergency to last through the end of this year. Congress quickly passed a law eliminating tariffs on imported medicines and medical supplies.

In March, the government issued a formal decree announcing a National Health Emergency, in effect until the end of this year. Under the decree, the government would reestablish supplies of medicine and other materials in public hospitals, guarantee supplies of medicine for vulnerable outpatients, guarantee access to medicines and supplies to prevent and treat infectious diseases and ensure access to medical services for recipients of social security benefits.

Under the emergency decree, the government has required doctors to prescribe drugs by their generic name as a cost-cutting measure. After a heated controversy, with the drug companies and groups allied to them opposing the move, the Congress voted at 2 a.m. on 28 August to make the measure law.

The government also set up an agency called Remediar to provide a selection of basic medications to clinics throughout the country. The medicines are to be given to people whose income is below the poverty line or who are not covered by any insurance plan. The programme is financed in part by US$ 110 million in redirected loans from the Inter-American Development Bank.

The agency is also charged with monitoring the sale of drugs to make sure that drug companies and pharmacists do not gouge customers. To this end, it has set up a toll-free telephone number to report overpricing and has requested the assistance of local chapters of Caritas International and the Red Cross.

Dr Mingrone said that under the emergency plan, committees have been set up in all hospitals to monitor the effect of the financial crisis on each illness they treat.

Argentina has a large number of well-educated health professionals who, despite the lack of resources are managing well, Mingrone said, and many are going the extra mile to help their patients.

The nurses in the maternity ward at Sáenz Peña Hospital in Chaco are now making cotton diapers by hand for new mothers who cannot afford to buy them. Other Argentines have devised creative ways to deal with the crisis. In July, volunteer doctors and pharmacists set up a street clinic for people without health coverage, the news agency EFE reported. In Mendoza, a special medical insurance system was established that allowed patients to pay with vouchers that doctors could use to "buy" other professional services through a national barter network called Red Global de Trueque. A supermarket chain in Santiago del Estero is allowing its customers to use points earned with its discount card to pay for medical appointments. ■

Terri Shaw, *Washington*

South Africa takes first steps to provide antiretrovirals

For the first time, the South African Cabinet has acknowledged that antiretroviral treatments for HIV/AIDS — which stop the HIV virus multiplying in the body — may be a good idea for the one million people needing them in the country, and hinted that if it they are affordable it may provide them. According to the Cabinet statement, "antiretroviral treatments can help improve the condition of people living with AIDS if administered at certain stages in the progression of the condition, and in accordance with international standards".

In the past, key government officials, particularly President Thabo Mbeki and Health Minister Manto Tshabalala-Msimang, have questioned the safety of antiretroviral drugs. In 2000, Mbeki told parliament that AZT was toxic, while this year Tshabalala-Msimang questioned the safety of nevirapine. Most AIDS activists have, understandably, been cautious in their welcome of the government's new position on the subject.

The Cabinet now says that it intends to tackle a number of challenges aimed at "creating the conditions that would make it feasible and effective to use antiretrovirals in the public sector". The challenges included the high cost of the drugs and the health infrastructure necessary to supervise and monitor the taking of these drugs. A task team made up of health and treasury department officials has been set up to investigate how much it would cost to introduce the drugs, the announcement, made on 10 October, adds.

Regulations allowing the importation and manufacture of cheap and generic drugs are to be introduced, and South Africa may work with a number of other African countries and pharmaceutical companies to manufacture affordable drugs on the continent. According to the Cabinet statement, the government plans to engage the private health care sector in discussion on the "costs, the impact, issues of resistance, compliance with drug prescriptions and so on" as a matter of urgency.

Treatment Action Campaign secretary Mark Heywood described the announcement as "significant", as it was the first time that government had made "concrete commitments" to extending access to antiretroviral drugs. The country's biggest trade union federation, the Congress of South African Trade Unions also welcomed the announcement as a step in the right direction but it recommended a wait-and-see approach: other government-appointed task teams have rejected various developmental initiatives on the basis of cost. Des Martins, chairman of the HIV Clinicians' Society, also said he wanted to see the commitment translated into action.

In April this year, the Cabinet announced that it would make antiretroviral drugs available as post-exposure prophylaxis to rape survivors. In addition, a court ruling ordered the government to extend its mother-to-child transmission prevention programme to all health facilities that have the capacity to give pregnant HIV-positive women nevirapine. However, delays in implementing these measures have resulted in widespread scepticism.

Meanwhile, HIV specialist François Venter estimates that universal provision of antiretroviral drugs will consume about 20% of South Africa's total health budget "which I don't think is excessive given that AIDS is the major cause of death in this country".

The government has submitted applications to the Global Fund to Fight AIDS, Tuberculosis and Malaria for support for care programmes, including antiretrovirals, in three of the country's provinces (KwaZulu-Natal, Gauteng and the Western Cape).

Kerry Cullinan, *Durban*