Answers to malaria

IT LOOKS LIKE THE TOOL TO CONTROL THE BUG HAS BEEN IDENTIFIED, SAYS **S ANANTHANARAYAN**

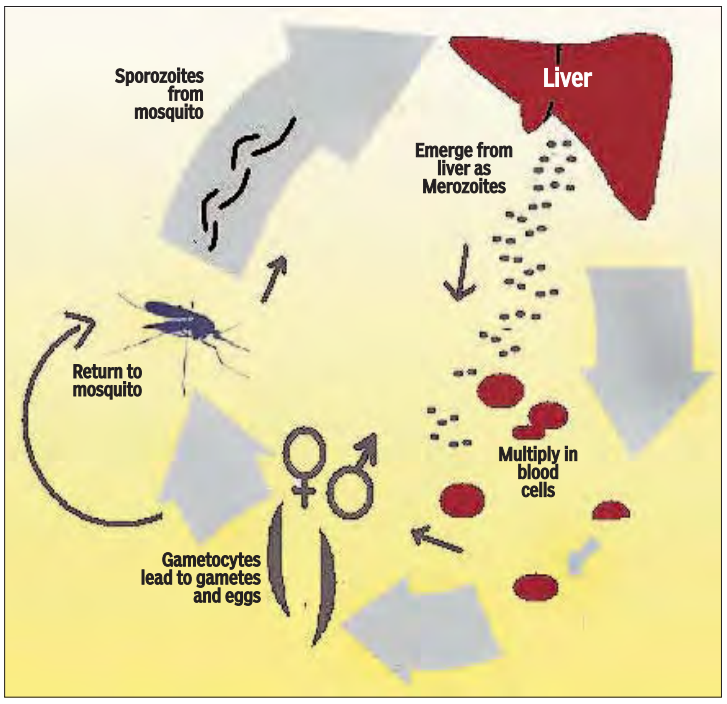
So far, the malaria parasite, a single-celled entity of a family called *Plasmodium*, has given the human race, particularly in the Tropics, an exceedingly hard time. The parasite is spread by mosquito bite and the hosts are vertebrates, like humans. At least 10 species of Plasmodium family affect humans and other species of the parasite also affect birds, reptiles and rodents. Usually, the female *Anopheles* mosquito infects people through its saliva, when it bites, for a blood meal. The parasite then breeds in the liver of the person bitten, to go forth and produce body symptoms that can go as far as coma or death and also to pass on to other humans, via other mosquitoes that may partake of a meal of the infected person's blood.

The parasite has proved well nigh impossible to control and some varieties have now become resistant to the most effective drugs. World Health Organisation data puts the number or malaria cases in 2010 at 219 million, with 666,000-1.2 million deaths, mostly of children in Africa. The two species that have serious effects, like death, on humans are *P.falsioparum* and *P.vivax*. All varieties are prevalent in the Tropics, with ample rainfall and higher temperatures, and they breed in stagnant water. Spraying and draining collections of water and the use of mosquito nets or repellants are measures of control, but with a rising population and crowded living spaces, civil authorities seem to be waging a losing battle.

In this context, the report of an international team, both industry- and university-based, in the journal *Nature* of discovery of a vulnerability of the malaria parasite at which drugs could strike for prevention, cure and control of transmission of the main varieties of the parasite that affect humans, is surely good news.

Infection

When the female mosquito bites, she transmits single-celled, self-propelled precursors of the infection into the victim's bloodstream. When these reach the liver cells, they multiply and produce another form of parasite that infects red blood cells. In the blood cells, this form rapidly multiplies and when the cell bursts with the increase in numbers of its invaders, they go forth to infect more blood cells. Waves of such escape of parasites are marked by waves of fever in the affected person. Some members of this form of the parasite grow into a form that leads to the creation of eggs that can start the cycle again. When a female mosquito bites and ingests this form of the parasite, the parasite matures in the mosquito's gut and results in fresh parasites of the first form, which migrate to the mosquito's salivary glands.



There are some standard treatment procedures and in the case of infection by P.vivax, both the blood cell stage as well as the earlier liver cell stage need to be treated, as P.vivax can stay dormant in the liver to cause delayed relapse. The only good drug for clearing the liver is *Primaquine*, but its continued use is not possible because of side effects and also because it is not so effective against the blood cell phase. As the mechanism of action of the drug is still not understood, well-directed search for radical cures has not taken place. What is needed, the authors of the paper in *Nature* observe, is to find and attack a target that is implicated in all the life-cycle stages of the parasite.

What they say

The authors report that a compound called *imidazopyrazine* is found to inhibit the action of an enzyme, *PI(4)K*, used by the Plasmodium parasite at all stages of its development. The discovery of this enzyme may be the first time a suitable target for gaining control of the spread of the virus has been identified.

The team carried out tests of the complicity of this enzyme at the different stages of the life-cycle — in incubation in the liver, the capacity for reinfection from stored remnants in the liver, the multiplication in the red blood cells and then the transmission of the reproducing variety to mosquitoes.

The first trial showed powerful blocking of one of the Plasmodium parasites that affects rodents by imidazopyrazine. The drug was found to be effective, in low doses, both as a preventive, when administered at the time of infection and also in clearing the infection when used after the infection had set in. And then, the liver-resident forms, which can cause delayed relapse, of another Plasmodium strain, were also cleared by small doses of the drug. P.vivax, which stays in the liver to cause relapse in humans, also showed sensitivity to imidazopyrazine, comparable to what was seen in the blood-cell stage of the more common P.falsiparum parasite.

During the blood cell stage also, it was found that the drug was able to block the development of numbers of the parasite that emerged from the liver. It was found that the drug interferred with the formation of viable instances of the second stage of the parasite, which multiplies in the blood cells. Infection of other blood cells, by the products of rupturing blood cells, was found to be very low in the case of drug-treated parasites, in comparison with controls, which shows that the drug brought about defects in the daughter products.

The last stage in the parasite life-cycle is that a small number of parasites in the blood cell stage differentiate into gametocytes, which are bodies that do not result in clinical symptoms but lead to egg cells and continuation of parasite line. These are ingested by mosquitoes that become capable of infecting victims of their bite through their saliva. These bodies are often not killed by the drug that may cure the patient of the disease, and the patient remains a source of infection to others or to himself/herself. The trials of the effect of the drug on the viability of gametocytes again showed that there was a marked reduction — and as for transmission via mosquito bite, this was completely blocked.

As for the complicity of the PI(4)K enzyme, the team examined the mechanism of the action of different imidazopyrazines by finding out just where some resistant forms of the parasite were different from the sensitive forms. Samples of the parasite were allowed to go through many generations and evolve into resistant forms. The genetic composition of the different forms were then compared and it was found that in all resistant forms, the change had occurred in the part of the genome, a single gene, which coded for PI(4)K. Different sub-trials, like allowing evolution without drug pressure, to lead to resensitisation as a result of correction of the defect in this same gene, established that it was PI(4)K that was the factor that resulted in imidazopyrazines having the inhibitor effect on the parasite.

The result is that PI(4)K has been identified as the drug target through which all the stages of the malaria parasite cycle can be addressed. "We anticipate that our findings will rapidly yield clinical candidates compatible with single exposure, radical cure and prophylaxis, a profile widely heralded as crucial for the success of worldwide malaria elimination efforts," the authors of the *Nature* paper say.

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ADVANTAGES FOR THE CELL

TAPAN KUMAR MAITRA EXPLAINS THE IMPORTANCE OF HIERARCHICAL ASSEMBLY

Biological structures are almost always constructed in a hierarchical manner, with sub-assemblies acting as important intermediates en route from simple starting molecules to the end products of organelles, cells and organisms. Consider how cellular structures are made. First, large numbers of similar, or even identical monomeric subunits are assembled by condensation into polymers. These polymers then aggregate spontaneously but specifically into characteristic multimeric units, which, in turn, can give rise to still more complex structures and eventually to assemblies that are recognisable as distinctive sub-cellular structures.

This hierarchical process has the double advantage of chemical simplicity and efficiency of assembly. To appreciate the chemical simplicity, we need only recognise that almost all structures found in cells and organisms are synthesised from about 30 small precursor molecules, which George Wald called the "alphabet of biochemistry".

This "alphabet" includes the 20 amino acids found in proteins, the five aromatic bases present in nucleic acids, two sugars and three lipid molecules. Given these building blocks and the polymers that can be derived from them through just a few different kinds of condensation reactions, most of the structural complexity of life can be readily elaborated by hierarchical assembly into successively more complex structures.

The second advantage of hierarchical assembly lies in the "quality control" that can be exerted at each level of assembly, allowing defective components to be discarded at an early stage rather than being built into a more complex structure that would be more costly to reject and replace. Thus, if the wrong subunit has been inserted into a polymer at some critical point in the chain, that particular molecule may have to be discarded, but the cell will be spared the cost of synthesizing a more complicated supramolecular assembly or even a whole organelle before the defect is discovered.

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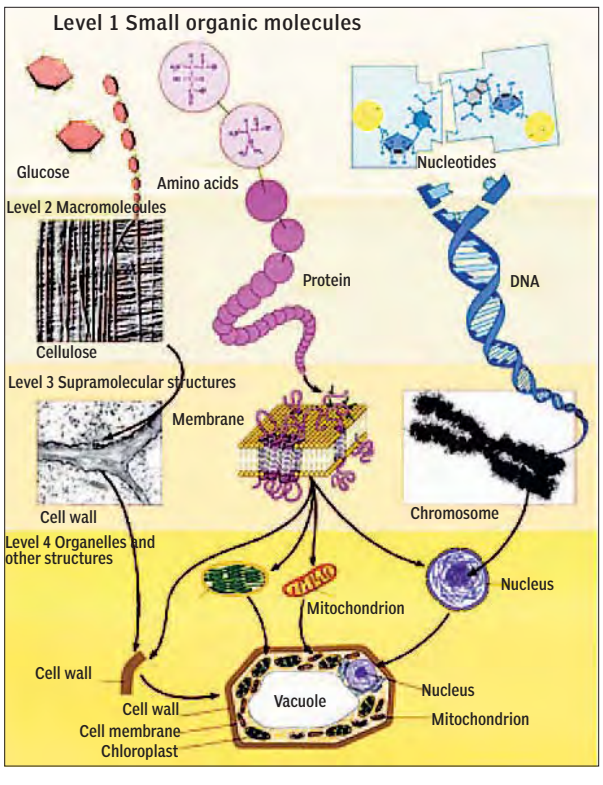


Hardwired difference

STEVE CONNOR REPORTS ON WHY 'MEN ARE BETTER AT MAP READING' AND WOMEN BETTER AT 'REMEMBERING A CONVERSATION'

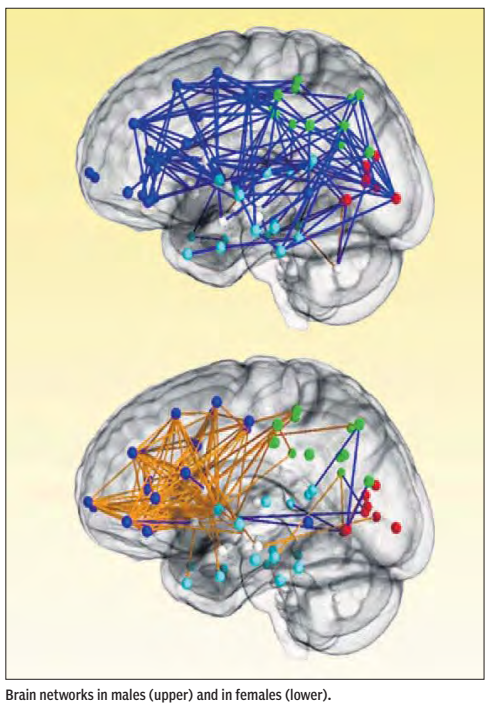
A pioneering study has shown for the first time that the brains of men and women are wired up differently, which could explain some of the stereotypical differences in male and female behaviour. Researchers found that many of the connections in a typical male brain run between the front and the back of the same side of the brain, whereas in women the connections are more likely to run from side to side between the left and right hemispheres of the brain.

This difference in the way the nerve connections in the brain are "hardwired" occurs during adolescence, when many of the secondary sexual characteristics such as facial hair in men and breasts in women develop under the influence of sex hormones, the study found. The researchers believe the physical differences between the two sexes in the way the brain is hardwired could play an important role in understanding why men are in general better at spatial tasks involving muscle control while women are better at verbal tasks involving memory and intuition.

Psychological testing has consistently indicated a significant difference between the sexes in the ability to perform various mental tasks, with men outperforming women in some tests and women outperforming men in others. Now there seems to be a physical explanation. "These maps show us a stark difference — and complementarity — in the architecture of the human brain that helps to provide a potential neural basis as to why men excel at certain tasks, and women at others," said Ragini Verma, professor of psychology at the University of Pennsylvania in Philadelphia. "What we've identified is that, when looked at in groups, there are connections in the brain that are hardwired differently in men and women.

Functional tests have already shown than when they carry out certain tasks, men and women engage different parts of the brain." The research was carried out on 521 females and 428 males aged between eight and 22 years. The brain differences between the sexes only became apparent after adolescence, the study found. A special brain-scanning technique called diffusion tensor imaging, which can measure the flow of water along a nerve pathway, established the level of connectivity between nearly 100 regions of the brain, creating a neural map called the "connectome", Professor Verma said. "It tells you whether one region of the brain is physically connected to another part of the brain and you can get significant differences between two populations. In women, most of the connections go between left and right across the two hemispheres while in men most of the connections go between the front and the back of the brain." she said.

The latest study, published in the *Proceedings of the National Academy of Sciences*, showed that the differences in the male and female "connectomes" develop during the same age of onset of the gender differences seen in psychological tests. The only part of the brain where right-left connectivity was greater in men than in women was in the cerebellum, an evolutionary ancient part of the brain that is linked with motor control.



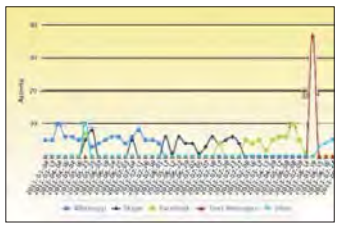
Brain networks in males (upper) and in females (lower).

THE INDEPENDENT

PLUS POINTS

Go spy

It's a secret agent's dream: one single piece of software that lets you into all of a "target's" communications, movements



The mSpy app provides detailed charts on a smartphone's activity, which users can browse remotely on a PC.

and personal notes. But this isn't some piece of top-secret NSA infrastructure. mSpy is a smartphone app that works on Android, Apple, Blackberry and Nokia phones — offering a staggering array of surveillance options.

The app — which works on a subscription basis starting at £24.99 a month — is described as being able to "run undetected on your child's or employee's cell phone and provide all of the necessary features for complete monitoring". Even in its most basic package, the app offers users a way to spy on phone calls, texts and emails, as well as providing a notification if the phone's owner switches SIM cards in an attempt to avoid detection.

For £44.99 a month, mSpy adds the ability to monitor communications on third-party apps, including Skype, Facebook, WhatsApp and iMessage. Both versions of the app allow the user to see the phone's Internet browsing history, what applications it has installed and view photos or videos taken.

Dark secret

Neuroscientist James Fallon studied dozens of brain scans of psychopathic killers looking for distinctive "flaws" that might mean such people were born to kill. Then one brain scan stopped him in his tracks. It showed all the "markers" of a classic psychopath. But it was Professor Fallon's own brain — included in the study as a comparison.

"I had been studying psychopaths and murderers — then I happened to discover that my own brain pattern and genetics were completely consistent with the people under study. I had to believe there was a mistake… But there had been no mistake. The scan was mine," he said. The discovery shook up his ideas about behaviour profoundly. "I am a successful, happily married man who married my childhood sweetheart and have a fully functioning family of three kids and five grandchildren."

In the months after the scan, though, members of his family revealed a secret history — a dark side of his own family. His mother said, "I hear you've been going around talking about psychopathic killers. And you're talking as if you come from a normal family." She revealed that there were no fewer than seven murderers in his family, including the notorious axe murderess Lizzie Borden. Other members of the family, though, had been conscientious objectors and pacifists.

Last chance

The spring spawning of coral on the Great Barrier Reef is a grand affair, with vast expanses of the Pacific Ocean turning red as millions of sperm and eggs are released in a spectacle that is visible from space. Last month, divers and snorkellers marvelling at the event were joined by scientists with a deadly serious purpose: to harvest billions of sperm and eggs and then freeze them in an effort to save corals in the World Heritage-listed reef from extinction.

The world's largest living organism has shrunk by about half over the past 30 years as a result of climate change, ocean acidification, pollution and crown-of-thorns starfish, which prey on coral. Some of its 400 or so species are endangered or threatened and marine biologists fear they could soon be wiped out. The establishment of a gene bank, using human fertility techniques, is a bold response by scientists seeking to conserve the reef, which runs for 1,600 miles off the Queensland coast. "We create a coral fertility clinic and we put them (the sperm and embryonic cells) in a bank, to hold them for now, but to use them in the future," said Mary Hagedorn from the Smithsonian Institution.

Dr Hagedorn, a marine biologist who perfected the techniques while working with coral in Hawaii, is liaising with Australian colleagues to deploy those techniques in the cause of conservation.

Sperm and cells from eight species have already been stored in the Dubbo bank, which is supervised by a team headed by

Rebecca Spindler. "We know the Great Barrier Reef is in deep, deep trouble," she said "We will never have as much genetic diversity again on the reef as we do right now. This is our last opportunity to save as much as we possibly can."

KATHY MARKS/THE INDEPENDENT