The National Defense Council Foundation
Issue Alert

ARTEMISININ NEW HOPE FOR MALARIA VICTIMS

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THE SCOURGE OF MALARIA

Malaria is one of the triumvirate of diseases that has devastated the developing world. Along with AIDS and Tuberculosis, it has reached pandemic proportions in Asia and Africa with some 120 million clinical cases reported annually. Although the vast majority of Malaria deaths occur in Africa, at lease 40% of the World's population has been exposed to the parasite. Indeed, it is estimated that 300 million people carry the parasite. This compares with around 40 million AIDS carriers and is exceeded only by Tuberculosis which may be carried by as much as one-third of the world's population.

What is particularly disturbing about Malaria, however, is that over the last century every time a new drug has been developed to combat it, the parasite has adapted and developed a resistance. In the 1950s quinine-based drugs such as Chloraquine and Primaquine proved highly effective in combating Malaria, but today, anywhere from 50% to 90% of new cases are proving resistant.

Over the past fifteen years, the older quinine-based drugs were replaced as the treatment of choice by Lariam (Mefloquine), a drug developed by the United States Army for soldiers serving in Vietnam. Lariam was first produced at the Walter Reed Army Institute of Research in 1963. Licensed to Swiss pharmaceutical giant Hoffman LaRoche, it was approved for general use in May of 1989. Each year, thousands of civilians traveling abroad as well as U.S. military and Peace Corps personnel take Lariam to protect them against Malaria.

PROBLEMS WITH LARIAM

However, like their predecessors, drugs such as Lariam are now also losing their effectiveness. Moreover, serious side effects have been associated with Lariam, including extreme neuropsychiatric disorders. These disorders are suspected of sparking a series of murders at Ft. Bragg, N.C. by soldiers returning from Afghanistan where they were administered the drug. Nor are those the only instances in which Lariam was suspected of causing violent or psychotic behavior.

Concern over the possible neuropsychiatric side effects of Lariam caused the FDA to require a change to the product's label in 2002 that reads in part:

"Mefloquine may cause psychiatric symptoms in a number of patients ranging from anxiety, paranoia and depression to hallucinations and psychotic behavior. On occasions these symptoms have been reported to continue long after mefloquine has been stopped. Rare cases of suicidal ideation and suicide have been reported though no relationship to drug administration has been confirmed."

What makes the concern over the growing drug resistance of the Malaria parasite an even more urgent problem is that the increase in global travel, especially to areas such as Africa and Southeast and Southwest Asia where Malaria is common raise the specter of its return to the United States. Other tropical diseases such as the West Nile Virus have already made there way here, and some fear it is only a matter of time before Malaria does so as well.

In addition, U.S. forces are increasingly being sent to regions where Malaria is prevalent. Therefore it is essential to have available a medication that is not only effective, but that also is relatively free of side effects.

But is there a solution?

AN HERBAL SOLUTION?

Surprisingly, an answer to the pressing question of finding an effective Anti-Malarial has been available for at least three decades, but it was largely ignored by Western medicine.

At about the same time the U.S. Army was looking for a new Malaria drug to give to soldiers fighting in Vietnam, the Chinese military was engaged in the same task to protect their own troops and those of North Vietnam. Their approach, however, was quite different.

China has a tradition of using herbal medicine that dates back over 2,000 years. In 1965, Chinese military researchers began looking at traditional herbal remedies to see if they could find one that was effective against the strain of Malaria endemic to Vietnam. In short order they hit on an herb known as "sweet wormwood."

Sweet wormwood had been used to treat a variety of illnesses in China for more than two millennia. Normally administered as a tea, it had no noticeable side effects and seemed quite effective. The Chinese military researchers were able to isolate the active ingredient in sweet wormwood, a substance called Artemisinin, and to develop a simple process to extract it.

The results were astounding.

ARTEMISININ'S EFFECTIVENESS

They found that Artemisinin was effective against all strains of Malaria, and more important, its therapeutic action was stunningly rapid. In one clinical trial, it was found to destroy 95% of the Malaria parasites in patients within twenty hours. The fever typically accompanying a Malaria infection was gone within eight hours. Moreover, there were no side effects. Other studies of Artemisinin confirmed its effectiveness and rapid action –

something particularly important for the treatment of very young children who account for 90% of all Malaria deaths.

But that wasn't all of the good news concerning Artemisinin.

Because sweet wormwood is easy to cultivate and because the extraction process to separate out the Artemisinin is simple, it was cheap to manufacture. In other words, it was the perfect answer to the developing world's Malaria pandemic.

Despite its promise, initially this new "miracle" cure was resisted by the World Health Organization, UNICEF and the other international organizations trying to combat global public health problems, largely due to a perceived lack of clinical investigation.

RESISTANCE AND REVERSAL

In 2002, Dr. Dennis Carroll, a health advisor to the Agency for International Development called Artemisinin *"... not ready for prime time ..."*

The World Bank and UNICEF objected to the herbal remedy claiming it was *"too expensive."* At the time, a dose of Artemisinin sold for around $2 whereas a single dose of Lariam costs from $4.50 to $6.00, making this statement somewhat incongruous

Suddenly, last April, Dr. Carroll reversed himself and became a cheerleader for Artemisinin.

How could this happen?

In large part it was due to the development of what is termed "*ACT"* or *"Artemisinin Combination Therapy."* Under this approach Artemisinin is combined with a pharmaceutical product – usually a drug called Lumefantrine that is produced by Novartis, the huge Swiss drug conglomerate. Novartis sells the combination under the

two different brand names: “Coartem” in the developing world and in the West under the brand name Riamet.

With the involvement of a major pharmaceutical firm, Artemisinin therapy quickly gained acceptance. In no small degree this may have because the involvement of a major Western pharmaceutical firm made scientists more willing to accept it as a treatment.

What is particularly important about Artemisinin becoming available, however, is that conventional pharmaceutical remedies are rapidly losing their effectiveness.

In Uganda, for example, a country which had not previously had a significant drug resistance problem, the number of Malaria cases not responding to existing pharmaceutical products rose from 6% in 2000 to 31% in 2003. Similar patterns of rapidly growing drug resistance are being experienced elsewhere.

RATIONALE FOR THE COMBINATION

The reason a “*combined drug therapy*” is recommended is the belief that using Artemisinin in combination with Lumefantrine will protect the herb against losing its effectiveness.

Use of this approach has generated enough confidence in the world health community that institutions such as the World Health Organization, the Global Fund for AIDS Tuberculosis and Malaria and the U.S. Agency for International Development are providing grants to farmers to grow more sweet wormwood so that sufficient supplies of the herb are available.

HOW ARTEMISININ WORKS

But how does Artemisinin work? The answer to this question may have implications for global health that go far beyond its effectiveness against Malaria.

Artemisinin contains a bioactive peroxide molecule. It is this molecule that is the key to its effectiveness against the Malaria parasite. Malaria grows in the body's erythrocytes, or red blood cells. Hemoglobin, a major component of red blood cells, contains large amounts of "*unbound*" or free iron. The iron plays a crucial role in the function of red blood cells to transport oxygen throughout the body. The peroxide molecule in Artemisinin reacts with the iron in the red blood cells to create free radicals that in turn destroy the parasite's membranes, killing it. This mechanism may be the reason why Malaria parasites are unable to develop a resistance to Artemisinin.

The belief that oxygen plays a key role in the Artemisinin anti-malaria mechanism has been reinforced by studies of derivatives of the substance that do not contain the peroxide molecule. These were found to be ineffective against malaria. Further, when other drugs such as miconazole and doxorubicin that also generate free radicals through an oxygen interaction were used in conjunction with Artemisinin, its effect was enhanced. Conversely when substances that retard free radical creation such as vitamin E were used in conjunction, its effect was reduced.

In a separate study where the antioxidant defenses of rats were manipulated, it was discovered that those with weaker antioxidant defenses were more resistant to the Malaria parasite, whereas those with enhanced antioxidant defenses were more vulnerable to the disease.

But why is it so important that Artemisinin transport oxygen to cells? The answer lies in the research of German Nobel Laureate Otto Warburg.

A POSSIBLE CANCER CURE?

Warburg won the Nobel Prize in 1928 for describing the way a cancer cell functions. A key element of his research was to establish that cancer cells were "*anaerobic*." That is to say that they required an **ABSENCE** of oxygen to survive. Since 1928, countless researchers have worked to find a way to transport oxygen to cancer cells. To date,

however, no successful therapy has been developed. This situation, however, may soon change.

Professor Henry Lai and Assistant Professor Narendra Singh of the University of Washington have been conducting in vitro experiments to determine the effectiveness of Artemisinin in fighting cancer. A study concerning their research published in the *Journal Life Sciences* described how the compound killed virtually all human breast cancer cells exposed to it within sixteen hours.

According to Dr. Lai, *"Not only does it appear to be effective, but it's very selective*." He continued *"it's highly toxic to the cancer cells, but has a marginal impact on normal breast cells."*

Dr. Lai has been investigating the potential of Artemisinin in regard to treating various types of cancer for over seven years with consistently promising results. He has developed a "*cocktail*" consisting of holotransferrin, a substance that binds with a cancer cells "*transferring receptors*," the part of the cell that absorbs iron and a water soluble form of Artemisinin. Cancer cells normally absorb much more iron than healthy cells. Therefore the chemical cocktail is attracted to the diseased cells and brings the Artemisinin along with it.

Although full-scale human trials have not been conducted as yet, in one animal trial, a dog with severe bone cancer was completely cured within five days of being given the Artemisinin cocktail.

According to Dr. Lai, Artemisinin could open the door to a whole new era of cancer treatment. Patients could be given a prescription for a pill they could take at home without the need to go through expensive hospital-based treatments.

> *"That would be very easy, and this [Artemisinin] could make that possible. The cost is another plus – at $2 a dose, it's very cheap. And with millions of people*

who have already taken Artemisinin for Malaria we have a track record showing that it's safe."

Dr. Lai continued:

"The fascinating thing is that this was something the Chinese used thousands of years ago. We simply found a different application."

The real question is not whether Artemisinin will eventually become part of the arsenal for fighting cancer as it has become part of the arsenal for fighting Malaria. Given the amazing results of Dr. Lai's research, it undoubtedly will. The real question is when.