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and Prophylaxis in Kenya

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Vaccines for the Prevention of Malaria. STO I. F. and Advanced Development

Western Kenya is endemic for some of the highest transmission rates of *Plasmodium falciparum* in the world. It therefore offers the most rigorous test of the efficacy of candidate vaccines. The planned field evaluation of the recombinant vaccine RTS,S-TRAP was not done because of equivocal Phase I results in American volunteers. The field population was maintained and a site for a new field clinic was obtained from the Ministry of Health.

Characterization of Protective Immune Responses against Malaria. STO I. F

Severe anemia is one of the most lethal complications of severe *P. falciparum* infection. Its pathogenesis is not well understood but research at USAMRU-K during 1998 provided increasingly convincing evidence that immunological factors play a basic role. Understanding these factors could lead both to better treatments and better vaccine design. Using an automated cell sorter to analyze red blood cells carrying novel fluorometric stains, it was determined for the first time that infected cells are significantly more susceptible to phagocytosis. It was also found that IgG is deposited on the surfaces of red blood cells in children with severe malaria induced anemia; at the same time CR1 and CD55 complement were reduced while Th1 and Th2 cytokines were increased, suggesting that the infected host's immune response plays a major role in gross hemolysis.

Malaria Drug Program. STO I. Q. and Advanced Development

The purpose of the US Army Medical Research Unit-Kenya antimalarial drug field testing unit is to conduct first field trials of candidate prophylactic antimalarials that have passed pre-clinical, phase I human pharmacology and initial human efficacy testing in the USA. WR 238605, now called tafenaquine, is a long-acting primaquine analogue that had been shown to prevent malaria when given during human challenge experiments at WRAIR. A field trial begun in 1997 in semi-immune Kenyan adults in rural western Kenya confirmed the promise of tafenaquine. Three different doses were tested (three days loading only, loading followed by 250 mg weekly, loading followed by 500 mg weekly) against placebo. Of the evaluable subjects, those who received 500 mg tafenaquine for only 3 days had a protective efficacy of 74% compared to placebo, those receiving 250 mg for 3 days followed by 250 mg weekly had a protective efficacy of 92% and those receiving 500 mg for 3 days followed by 500 mg weekly had a protective efficacy of 94%. A trial planned at the Brooke-Bond Ltd tea plantations was aborted two weeks before enrollment was to begin when the parent company, Unilever (London), rescinded permission. The reason has not been ascertained.

Malaria resistance to chloroquine and Fansidar began in Africa much later than in Asia. The current extent and degree of specific susceptibilities is unknown, a matter of concern when advising preventive measures to be taken by US forces deployed to the area. After extensive changes in management, the laboratory established in 1998 to provide the first in vitro testing for resistance in East Africa finally began operation. More than 100 field specimens have been successfully cultured and tested. Standardization and training of new technical staff were going on by the end of 1999, but preliminary results indicate resistance to chloroquine and unexpected tolerance to artemesins.

Vector Studies. STEP I. U.

Malaria transmission in much of Africa is seasonal, with intense transmission during the

rains but little during the intervening dry periods. The reason appears to be the disappearance of the major vector *Anopheles gambiae* during the dry season. Many hypothesis have been advanced to explain this disappearance. Using an advanced global positioning system, the area used for vaccine testing was precisely mapped to show fluctuations in available breeding sites, malaria incidence, and mosquito abundance. It has been found that during the dry season transmission is confined to houses close to swamps where the vector *A. funestus* breeds, but as the rains start and puddles form *A. gambiae* predominates.

A study sponsored by USAMRU-Kenya that investigated confirmed malaria in children visiting clinics in the city of Nairobi found that the parents of 40% of cases claimed no travel outside during the life of the child. Most cases appeared to originate in the extensive slum of Kibera and a study to confirm transmission was begun.

#### STEP H. HIV Vaccine

CY99 marked the first year of USAMRU-Kenya involvement in the DoD's retrovirology program. An unbudgeted \$100 K was allocated to set up laboratories and begin systematic, country-wide genotyping of HIV clades. Blood donor units found by hospitals to be infected (and therefore to be destroyed) was used, DNA extracted, and typed. Nearly 300 units were processed, predominately from western Kenya. Results are being tabulated and collection sites are being expanded to central and eastern Kenya. In the mean time, \$250 K in FY00 money was made available to develop a 5,000 person cohort study, with extensive immunological parameters, at the African Highland Produce tea plantation, to measure incidence. This study has already produced evidence of sub-cladistic variation.

#### Emerging Infectious Diseases

In collaboration with the WHO Regional Virus Reference Center, we screened archived blood collected from undiagnosed fever cases presenting at the Oxford University clinic at Kilifi, on the Indian Ocean Coast. So far, three confirmed dengue-2 have been found, including one isolation that has been sequenced at Ft. Collins by the CDC; it was found to be identical to the last confirmed case from Kenya, found 19 years earlier. This provides strong evidence that contrary to dogma, dengue is routinely transmitted on the coast and is a significant cause of illness among children. Plans were made to extend the FUO study to a 24 clinic sentinel network.

#### COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENTS

"A Phase III Randomized Double-blind Placebo Controlled Evaluation of Weekly WR238605 (tafenaquine)"

CRDA with Smith Kline Beecham Ltd, UK

PI: COL G. D. Shanks; AI: LTC B. Smoak

Purpose: to evaluate prophylactic efficacy of tafenaquine against falciparum malaria

"Randomized Phase I Study to Evaluate the Safety, Reactogenicity, etc of RTS,S vs Energix B in Semi-Immune Adults in Western Kenya"

CRDA with Smith Kline Beecham, Belgium

PI: LTC J. A. Stoute; AI: LTC C. Mason

Purpose: to evaluate the efficacy of RTS,S vaccine in preventing malaria in an area of high incidence.

## GRANTS, CONTRACTS, ETC.

Malaria Ecology, Transmission, Immunology, Parasitology, and Prophylaxis in Kenya.

PI: Dr. Davy Koech, Kenya Medical Research Institute

Funded by U.S. Army Medical Research and Materiel Command

\$1,038,380 (1 December 1995 - 31 December 1998)

- Cooperative Agreement between MRMC and KEMRI for research on malaria and other infectious agents
- Provides infrastructure and personnel support
- Work conducted under STO/STEPs F, Q, U, A, P, and GEIS

## PLANS AND STRATEGIES FOR THE FUTURE

USAMRU-K began a three year renewal of its Cooperative Agreement with KEMRI in January 1999. The prospects for cutting edge research are greater than ever before but several crucial issues may severely jeopardize progress.

The main thrust will continue to be against malaria, with lesser efforts devoted to several other infectious diseases of acknowledged military significance. A Phase II trial of RTS,S malaria vaccine will be done and work on the role of cell mediated immunity and hemolytic immunity in severe malaria will continue. A Phase III trial is planned of tafenaquine. The extraordinary resources of the new highland site will be exploited for studies on climate and malaria. New efforts have been funded for HIV, leishmaniasis, tuberculosis diagnostics, vector biology, and emerging disease surveillance.

However, the transfer of four officers in 1999, only one of whom - a replacement for the clinical laboratory officer - has been designated, will likely impede exploitation of these opportunities. Aggravating the personnel problems, salaries for Kenyan technical staff recede ever farther behind those of other Kenyan research organizations, making retention and recruitment difficult; currently USAMRU-K has no Kenyan PhD or MD staff.

## Publications

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