



**FACULTY OF TROPICAL MEDICINE
MAHIDOL UNIVERSITY
ANNUAL REPORT 1999**



**Faculty of Tropical Medicine
Annual Report 1999**

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The Editors would like to thank all contributors, Departments and Units for providing information for the preparation of this Annual Report

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Foreword

This year now closing, 1999, has been a very significant and successful one for the Faculty of Tropical Medicine. I would like

to convey my congratulations and sincere thanks to all members of the Faculty for their hard work and their dedication, and not least for their expertise, energy and creativity, without which this year would not have been so fruitful.

In the following Annual Report for 1999, it is my great pleasure to report the activities undertaken by our staff and students, and the activities of the SEAMEO TROPMED Regional Centre for Tropical Medicine.

This year, we have continued our tradition of high achievement in research, teaching, training and health services. One of the major initiatives seen this year has been the designation of the Faculty as the Training Centre for Parasite Control for Asia, in collaboration with other agencies, including SEAMEO-TROPMED, under the title "The Asian Centre of International Parasite Control" (ACIPAC).

However, this past year was not without sadness, with the loss of the co-founder of the Faculty of Tropical Medicine, Professor Emeritus Khunying Tranakchit Harinasuta, on 29 April 1999. By contrast, we were later greatly heartened to witness her son present the inaugural "Professor Emeritus Khunying Tranakchit Harinasuta Award" in October 1999 at the DTM&H Graduation Ceremony.

Also this year, 11 long-standing and well-respected members of the Faculty chose to take early retirement. I know we will miss them all and that we wish them all the best in their retirement.

Once again I convey my sincere congratulations and thanks to all members of the Faculty for their efforts throughout 1999.

Professor Sornchai Looareesuwan

*Dean, Faculty of Tropical Medicine
Mahidol University, Bangkok, Thailand*

Editor's Overview

The Faculty of Tropical Medicine, Mahidol University, plays an important role in promoting the University's excellence in teaching and training, research, and clinical care. The Faculty was established by the Thai Government on 5 April 1960. The Faculty joined the SEAMEO TROPMED Project in 1967 and was designated by the Thai Government as the TROPMED National Center of Thailand. In 1994, national status was elevated to the regional level, thus becoming SEAMEO TROPMED Regional Center for Tropical Medicine (TROPMED/Thailand). In the fiscal year 1998/1999 (FY1998/1999), there were 377 government service staff and 341 employees affiliated in 11 departments, a hospital and other supporting units, of whom 89 were academic staff comprising 10 Professors, 27 Associate Professors, 28 Assistant Professors, and 24 Lecturers.

In continuing to deal with the consequences of the national economic crisis, which has resulted in budget stringencies since 1997, the Faculty of Tropical Medicine sees its key roles as being the provision of high quality education and training, high quality research in the field of tropical medicine and its allied disciplines, the dissemination of the results of such research, and the provision of excellent clinical care and appropriate consultancy services. Healthcare services are provided by the Hospital for Tropical Diseases, a 250-bed hospital with an Intensive Care Unit, Center for Laboratory Diagnosis of Parasitic Infections, and other facilities for the management of endemic tropical diseases. The hospital is world renowned for the treatment of malaria.

Over the years, the Faculty of Tropical Medicine has retained its strengths in tropical medicine, health science and basic science. Five international post-graduate programs are offered to doctors, researchers, medical personnel and professionals concerned with tropical medicine and public health. They are: the graduate Diploma in Tropical Medicine and Hygiene; the Master of Clinical Tropical Medicine and the Master of Science in Tropical Medicine; the Doctor of Philosophy in Tropical Medicine and the Doctor of Philosophy in Clinical Tropical Medicine. Overall, 1,979 students from 42 countries have graduated, and in FY1998/1999 there were 131 enrolled students from 17 countries: Australia, Austria, Bangladesh, Cambodia, India, Japan, Lao PDR, Malaysia, Myanmar, Nepal, Pakistan, the Philippines, Russia, Singapore, Thailand, the United States of America and Vietnam.

The Faculty has also conducted 3 joint courses in collaboration with other institutions, including those with: the Liverpool School of Tropical Medicine, training postgraduates in both institutions for Master's courses in Tropical Paediatrics since 1993/1994; the Austrian Society of Tropical Medicine and Parasitology in jointly offering the 4-month program leading to the Austrian Diploma in Tropical Medicine; and the Faculty of Public Health and the Faculty of Medicine, Ramathibodi Hospital, Mahidol University in an international program leading to the Master of Science in Medical Epidemiology. The international elective program in tropical medicine has also been offered to final year medical students since 1994/1995 and continued in 1999 with a total of 11 students, 8 from Austria and 3 from the United Kingdom.

The Faculty has ongoing **collaborative activities** in teaching, research and academic services with more than 25 universities and institutions from 13 countries: Australia, Austria, Canada, France, Germany, Indonesia, Japan, Malaysia, the People's Republic of China, the Philippines, Switzerland, the United Kingdom, and the USA. Examples of collaborative activities are: those with the Free University of Berlin, Germany; the University of Calgary in Canada; the Nuffield Department of Medicine, University of Oxford, the Liverpool School of Tropical Medicine and the Wellcome Trust, UK; the University of Innsbruck, Austria; the Queensland Institute of Medical Research and James Cook University of North Queensland, Australia; the Pasteur Institute and Department des Maladies Infectieuses et Médecine Tropicale, Groupe Hospitalier Pitié Salpêtrière, France; the Japan Association for Parasite Control (JAPC) and the Asian Parasite Control Organization (APCO). In 1998/1999, international linkages were increased further, with 3 Memoranda of Understanding (MOU) being signed between SEAMEO TROPMED Network, the Faculty of Tropical Medicine as TROPMED/Thailand and: the University of Tsukuba, Japan; the Centre for Animal Parasitology, Canadian Food Inspection Agency, Saskatoon, Canada; and the Liverpool School of Tropical Medicine, UK. In the year under review, there were 150 visitors from 20 countries and organizations who visited the Faculty for collaborative research work, consultative services, specimen and information exchange and to give seminars and conferences.

The Faculty, in conjunction with other National Centers for Tropical Medicine and Public Health in Southeast Asia and some international institutions and organizations, annually conducts national, regional and international training courses, seminars, meetings and workshops that have directly benefited over 2,324 participants, covering various subjects in tropical medicine, public health and the medical sciences. In FY1998/1999, the Faculty organized and hosted 14 national, regional and international training courses, workshops and meetings with 631 participants from 26 countries.

The Faculty has organized the annual **Joint International Tropical Medicine Meeting (JITMM)** since August 1997. The objectives of the Meeting are: to foster a dialogue on scientific advancement in tropical medicine; to serve as a venue for doctors and scientists to exchange ideas, leading to collaborative research and joint efforts to raise awareness, to face the challenges of emerging and reemerging tropical diseases. In 1999, the JITMM was held at the Century Park Hotel, Bangkok, between 4-6 August 1999, and was attended by 531 participants from 25 countries.

The Faculty, together with the Parasitology and Tropical Medicine Association of Thailand, the TROPMED Alumni Association and SEAMEO TROPMED is currently organizing the **“3rd Seminar on Food-borne Parasitic Zoonoses: Food- and Water-Borne Parasitic Zoonoses in the 21st Century (FBPZ3)”**, which is to be held concurrently with JITMM 2000, between December 6-8, 2000 at the Royal River Hotel, Bangkok.

The Faculty is extensively involved in national and international programs to control tropical diseases. In the year under review, 132 research projects were conducted by staff of the Faculty. These research projects were directed towards the solution of common health problems in Thailand and Southeast Asian countries, including the following: malaria, amebiasis, liver fluke infections, paragonimiasis, soil-transmitted helminthiasis, schistosomiasis, filariasis, dengue, Japanese encephalitis, rabies, HIV/AIDS, food-borne mutagens and carcinogens, nutritional problems, diarrhea and enteric fever, melioidosis, leprosy, diagnosis of tropical diseases, vaccine trials, vaccine development and vector control. Results of the studies were well-recognized and published mainly in international journals, with 114 publications in FY1998/1999. Many staff members of the Faculty received awards in recognition of their outstanding research work from both national and international institutions and organizations. Of special note was the award to **Prof. Wanpen Chaicumpa** of the **“1999 Outstanding Scientist Award”, by His Majesty the King**, for her achievement in immunology. Prof. Wanpen and her colleagues also received the **“Best Research Work in Chemistry and Pharmaceutical Science Award”** from the National Research Council, Ministry of Science, Technology and Environment, Thailand.

HIV/AIDS Vaccine Trials

The Vaccine Trial Centre (VTC) of the Faculty is participating in trials to evaluate the **safety and immunogenicity of Aidsvax™ B/E Vaccine in Bangkok, Thailand**. This is a collaborative study between the Vaccine Trial Centre and the Bangkok Metropolitan Administration. As a part of the Bangkok Vaccine Evaluation Group, the VTC began the phase III efficacy trial in the fourth quarter of 1998, continuing into 1999.

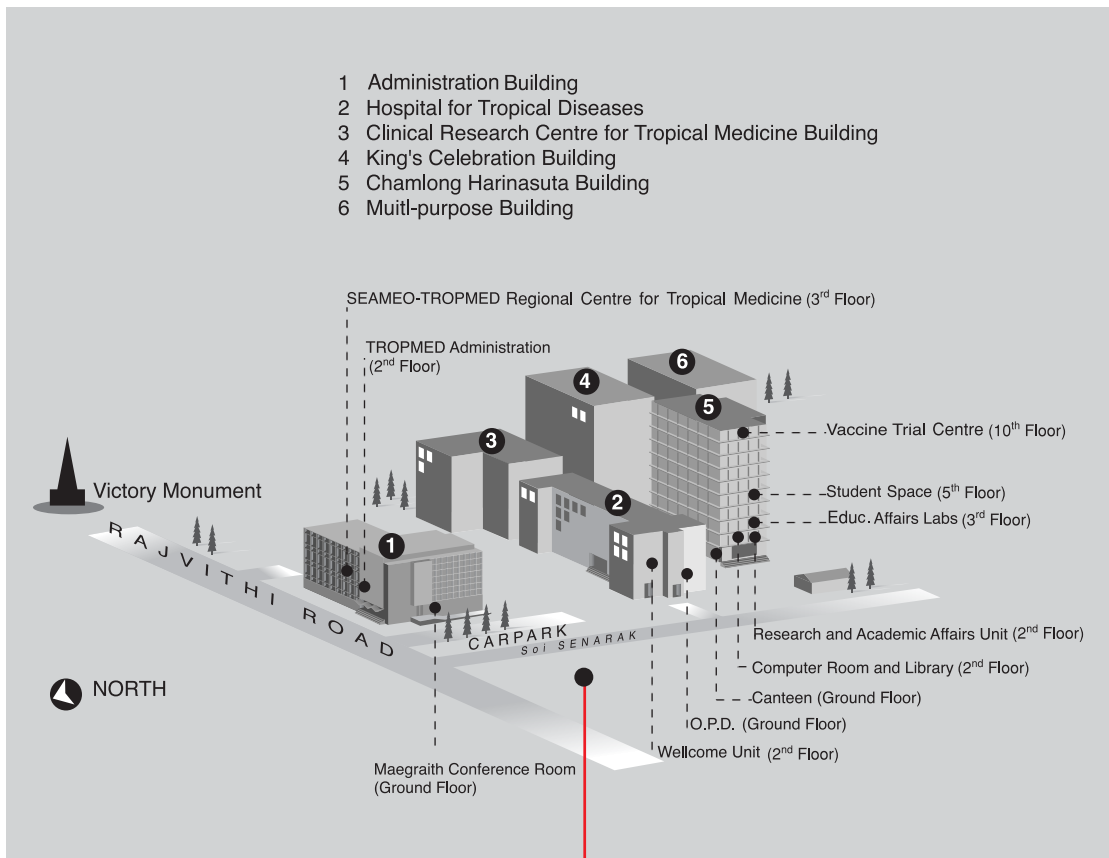
Hashimoto Initiative on Global Parasite Control

Former Japanese Prime Minister, Mr. Hashimoto, proposed the initiative on “global parasite control” at the G8 Summit Meeting in 1997. In 1999, the Faculty of Tropical Medicine, Mahidol University, was selected as the Training Centre for Parasite Control for Asia, and preparations are currently underway to put the initiative into full operation, in collaboration with other agencies, under the name **“The Asian Centre of International Parasite Control” (ACIPAC)**.

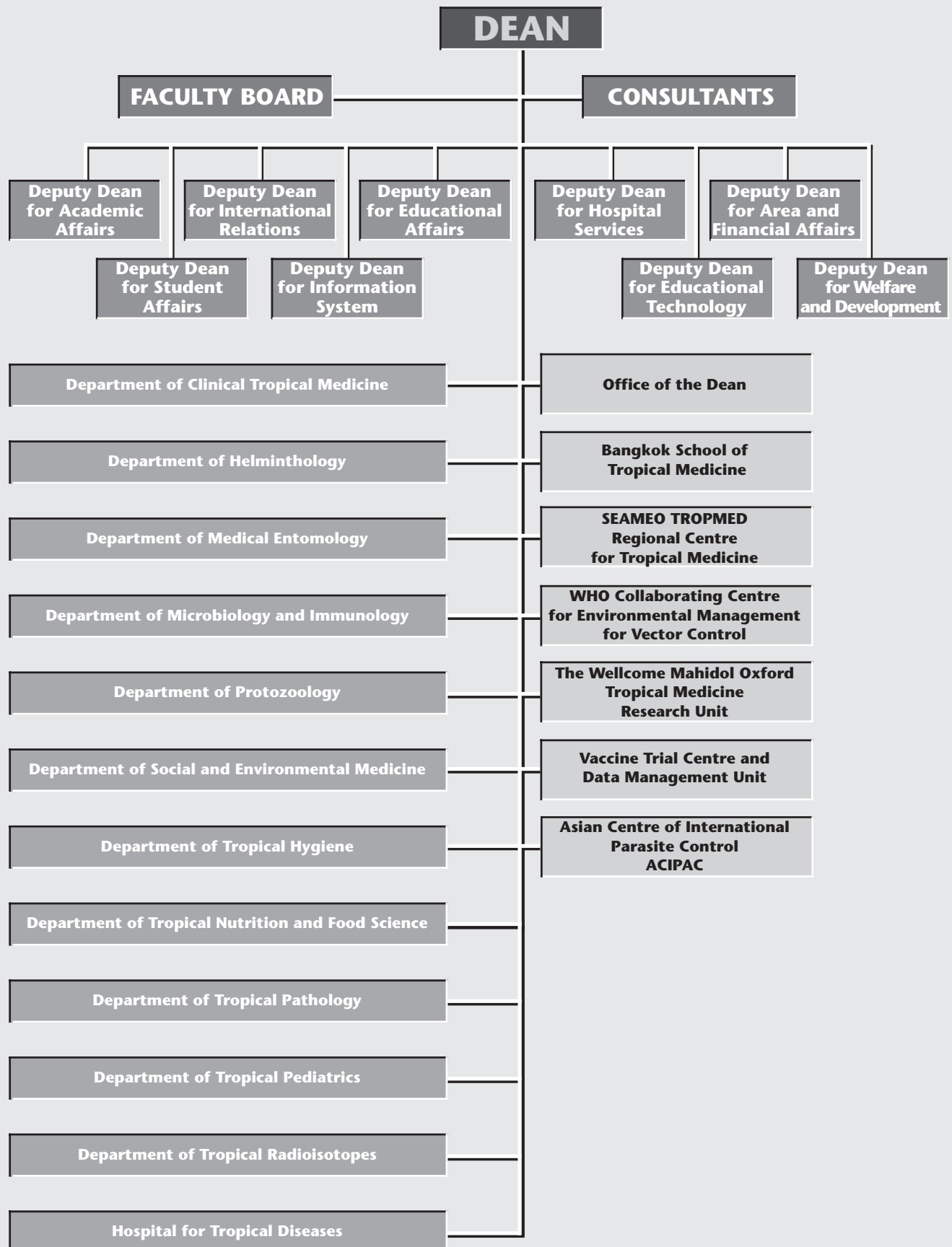
The 1999 Annual Report of the Faculty of Tropical Medicine covers research activities, summarizing research fields of interest, followed by the research progress made in the last year of each Department and Unit, research abstracts, post-graduate programs, students and their theses, short training courses and academic services. We trust that this Annual Report gives a round and accurate picture of the research, academic, and service activities of the Faculty between October 1, 1998 and September 30, 1999.

Associate Professor Jitra Waikagul
Assistant Professor Achara Asavanich
Editors

- 1 Administration Building
- 2 Hospital for Tropical Diseases
- 3 Clinical Research Centre for Tropical Medicine Building
- 4 King's Celebration Building
- 5 Chamlong Harinasuta Building
- 6 Muilt-purpose Building



Organization and Administration of the Faculty of Tropical Medicine, Mahidol University, Thailand



Dean, Deputy Deans, and Assistant Deans



Dean
Prof. Sornchai Looareesuwan



Deputy Dean for International Relations
Assoc. Prof. Suvanee Supavej



Deputy Dean for Academic Affairs
Assoc. Prof. Jitra Waikagul



Deputy Dean for Hospital Services
Prof. Polrat Wilairatana



Deputy Dean for Welfare and Development
Assoc. Prof. Somjai Leemingsawat



Deputy Dean for Area and Financial Affairs
Assist. Prof. Thaiyooth Chintana



Deputy Dean for Educational Technology
Assoc. Prof. Chamnarn Apiwathnasorn



Deputy Dean for Educational Affairs
Assist. Prof. Yaowalark Sukthana



Deputy Dean for Information System
Assist. Prof. Kasinee Buchachart



**Deputy Dean
for Student Affairs**
Dr. Chotechuang Panasoponkul



**Assistant Dean for Areas
and Maintenance**
Asst. Prof. Thongchai Deesin



**Assistant Dean
for Environment**
Assoc. Prof. Kanjana Hongtong



**Assistant Dean
for International Relations**
Asst. Prof. Parnpen Viriyavejakul



**Assistant Dean
for Special Activities**
Miss Kobsiri Chalermrut



Secretary of the Faculty
Mrs. Vorapan Singhsilarak

Consultants

No.	Name
1.	Prof. Emeritus Chamlong Harinasuta
2.	Prof. Emeritus Khunying Tranakchit Harinasuta
3.	Prof. Emeritus Danai Bunnag

No.	Name
4.	Prof. Emeritus Sommaiya Vilairatna
5.	Prof. Emeritus Mukda Trishnananda
6.	Prof. Emeritus Prayong Radomyos
7.	Col. Sriwatana Chitchang

Visiting Professors

No.	Name	Country
1.	Prof. Walther H. Wernsdorfer	Austria
2.	Prof. Ralf Clemens	Belgium
3.	Prof. Frank P. Schelp	Germany
4.	Prof. Gunther Wernsdorfer	Germany
5.	Dr. Frédéric Gay	France
6.	Prof. Kenji Hirayama	Japan
7.	Prof. Masamichi Aikawa	Japan
8.	Assoc. Prof. Dr. Shigeyuki Kano	Japan
9.	Prof. Somei Kojima	Japan
10.	Prof. Tozo Kanda	Japan

No.	Name	Country
11.	Prof. C.P. Ramachandran	Malaysia
12.	Dr. P.F. Beales	Switzerland
13.	Dr. Chev Kidson	Thailand
14.	Dr. E. B. Doberstyn	Thailand
15.	Dr. David Warrell	UK
16.	Prof. Herbert M. Gilles	UK
17.	Dr. Gary M. Brittenham	USA
18.	Prof. John H. Cross	USA
19.	Dr. Karl A. Western	USA
20.	Dr. Stephen L. Hoffman	USA

Faculty Board

No.	Name	Position
1.	Prof. Sornchai Looareesuwan	Dean
2.	Prof. Polrat Wilairatana	Deputy Dean for Hospital Services
3.	Assoc. Prof. Suvanee Supavej	Deputy Dean for International Relations
4.	Assoc. Prof. Jitra Waikagul	Deputy Dean for Academic Affairs
5.	Assoc. Prof. Somjai Leemingsawat	Deputy Dean for Welfare and Development
6.	Assoc. Prof. Chamnarn Apiwathnasorn	Deputy Dean for Educational Technology
7.	Assist. Prof. Thaiyooth Chintana	Deputy Dean for Area and Financial Affairs
8.	Assist. Prof. Yaowalark Sukthana	Deputy Dean for Educational Affairs
9.	Assist. Prof. Kasinee Buchachart	Deputy Dean for Information System
10.	Dr. Chotechuang Panasoponkul	Deputy Dean for Student Affairs
11.	Assist. Prof. Thongchai Deesin	Assistant Dean for Areas and Maintenance
12.	Assoc. Prof. Kanjana Hongtong	Assistant Dean for Environment
13.	Assist. Prof. Parnpen Viriyavejakul	Assistant Dean for International Relations
14.	Miss Kobsiri Chalermrut	Assistant Dean for Special Activities
15.	Assoc. Prof. Vanida Deesin	Head of Department of Medical Entomology
16.	Assoc. Prof. Pornthep Chanthavanich	Head of Department of Tropical Pediatrics
17.	Assoc. Prof. Pramuan Tapchaisri	Head of Department of Microbiology and Immunology
18.	Assoc. Prof. Malinee Thairungroj	Head of Department of Helminthology
19.	Assoc. Prof. Varaporn Suphadtanaphongs	Head of Department of Protozoology
20.	Assoc. Prof. Emsri Pongponrat	Head of Department of Tropical Pathology
21.	Assoc. Prof. Supranee Changbumrung	Head of Department of Tropical Nutrition and Food Science
22.	Assist. Prof. Channarong Sanghirun	Head of Department of Tropical Radioisotopes
23.	Assist. Prof. Pratap Singhasivanon	Head of Department of Tropical Hygiene
24.	Assist. Prof. Piyarat Butraporn	Head of Department of Social and Environmental Medicine
25.	Assoc. Prof. Wichai Supanaranond	Head of Department of Clinical Tropical Medicine
26.	Prof. Wanpen Chaicumpa	Elected Member
27.	Assoc. Prof. Surang Tantivanich	Elected Member
28.	Assoc. Prof. Dwip Kitayaporn	Elected Member
29.	Assist. Prof. Achara Asavanich	Elected Member



**Current Research
Activities
and Abstracts**

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Vichitra Pornkulprasit



Udomsak
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Chuanpit Preechawuthiwong B.A. (Political Science)



Varunee Desakorn



Chuanpit
Preechawuthiwong

CURRENT RESEARCH ACTIVITIES

The Department has published more than 300 papers and has continued to pursue its mission in three major activities, teaching, research and services. The Department embarked upon clinical research on several major tropical infectious diseases.

Malaria research activities have focused on clinical trials, pathophysiology, clinical pharmacology and clinically related laboratory studies. Staff of the Department studied not less than 2,500 admitted cases of this disease. It was found that 45% were falciparum malaria, 52% were vivax malaria, 2% mixed infections of the two above, a few cases of malariae malaria and occasionally cases of ovale malaria. The major focus is on clinical trials of multidrug resistant falciparum malaria in uncomplicated and complicated cases. Combinations of various antimalarial drugs were carried out continuously; halofantrine, mefloquine, quinidine, amodiaquine, artemether and artesunate in combination with mefloquine. We found that sequential treatment with artesunate or artemether followed by mefloquine is effective, well-tolerated and suitable as an alternative treatment for multidrug resistant malaria.

Besides extensive clinical studies, we also carried out interdepartmental and institutional collaborative studies of antigen in cerebral and non-cerebral malaria patients, of lymphocyte subpopulations during acute and convalescence phases of malaria, and qualitative and quantitative polymerase chain reaction to predict *Plasmodium falciparum* treatment failure. Pathophysiologic alteration in malaria has been widely investigated. Interesting results were the dynamic alteration in splenic function during acute falciparum malaria, in erythrocyte survival following clearance of malaria parasites, defective production of and response to IL-2 in acute falciparum malaria, cytoadherence and ultrastructure of *Plasmodium falciparum* infected erythrocytes from splenectomized patients and hepatic blood flow and metabolism in severe falciparum malaria.

Studies of stage specificity of quinine, chloroquine, mefloquine, artesunate, artemether and halofantrine were carried out in vivax malaria. The antimalarial efficacy of tetracycline, doxycycline, rifampicin and azithromycin was also studied.

Other common parasitic diseases including amoebiasis, opisthorchiasis, paragonimiasis, cysticercosis, scrub typhus, salmonellosis, and the clinical manifestations of HIV/AIDS with parasitic infections have been studied in many aspects.

The titles of current departmental research activities are as follows:

1. Pharmacokinetics and pharmacodynamics of the combination dihydroartemisinin-mefloquine in healthy subjects with uncomplicated falciparum malaria.
2. Immunogenetic analysis of uncomplicated and severe malaria defined clinically and pharmacologically.
3. Gastric emptying in patients with acute falciparum malaria.
4. Pharmacokinetics and pharmacodynamics of AZT and AZT-triphosphate in healthy subjects, asymptomatic HIV-positive, and symptomatic AIDS patients.
5. Study on stage development of *Plasmodium falciparum* *in vitro*.
6. Pharmacokinetics and dose-finding studies of the combination artemether/proguanil in healthy subjects and patients with uncomplicated falciparum malaria.
7. Clinical study to find an effective regimen for the treatment of uncomplicated falciparum malaria in rural areas.
8. Emergencies of liver fluke infections during the dry season : Lam-Takong and Mae-Kwnang National Reservoirs.
9. Neurotoxicity of oral artemether in an animal model.
10. Dissolution tests for fast-release dihydroartemisinin compound tablets.
11. Comparative assessment of *in vivo* and *in vitro* sensitivity of *Plasmodium vivax* to chloroquine.
12. Investigation of the response of *Plasmodium falciparum* to a combination regimen of artesunate plus mefloquine in Mae Sot District, Tak Province.
13. Bioequivalence of mefloquine when given as Mepha® and Alloquin.
14. Study on partition of and antimalaria mefloquine.
15. Bioavailability and bioequivalence of suppositories leval artesunate and artemether in healthy volunteers.
16. Host factors related to severe and complicated falciparum malaria.

International institutional linkages

1. Nuffield Department of Clinical Medicine, University of Oxford, England.
2. Department of Medicine, George Washington University Medical Center, Washington DC, USA.
3. Hahnemann University, Philadelphia, USA.
4. Case Western Reserve University, USA.
5. Department of Epidemiology, University of Michigan, USA.
6. Queensland Institute of Medical Research, University of Queensland, Brisbane, Australia.
7. Department of Medicine, University of Toronto, Canada.
8. Department of Microbiology and Infectious Diseases, Faculty of Medicine, University of Calgary, Canada.
9. Wellcome Trust Research Laboratories, Nairobi, Kenya.
10. Department of Infectious Diseases, Ullevaal Hospital, University of Oslo, Norway.
11. Department of Infectious Diseases, Faculty of Medicine, University of Vienna, Austria.
12. Department of Tropical Medicine and Specific Prophylaxis, Faculty of Medicine, University of Vienna, Austria.
13. Austrian Society of Tropical Medicine and Parasitology, Vienna, Austria.

Training course

Austrian Diploma Course for Tropical Medicine, 4-29 January 1999

The Austrian Society of Tropical Medicine and Parasitology and the Faculty of Tropical Medicine, have jointly offered the course leading to the "Austrian Diploma in Tropical Medicine" since 1992. This 4-month annual programme aims to enrich Austrian medical doctors' understanding of the clinical, biological, epidemiological and social dimensions of tropical diseases, particularly in Southeast Asia. Course participants attend lectures in Austria for 3 months followed by one month clinical practice at the Bangkok Hospital for Tropical Diseases and other hospitals in Bangkok in the second part of the programme. They also visit some hospitals in the northeast of Thailand.



Abstracts

THERAPEUTIC RESPONSES TO DIFFERENT ANTIMALARIAL DRUGS IN PATIENTS WITH VIVAX MALARIA

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JA Simpson^{1,2}, S Vanijanonta¹,
R Clemens³, S Loaresuwan¹,
NJ White^{1,2}**

¹ Department of Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

² Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, Oxford University, UK.

³ SmithKline Beecham, Rixensart, Belgium.

Therapeutic responses to the eight most widely used antimalarial drugs were assessed in 207 adult male patients with *Plasmodium vivax* malaria. Based on parasite clearance time (PC_T) and parasite reduction ratio (PRR), the antimalarials showed three grades of activity which were highest for artesunate and artemether, followed by chloroquine and mefloquine, and were lowest for quinine, halofantrine, primaquine and pyrimethamine-sulfadoxine. Except for five patients who failed following treatment with pyrimethamine-sulfadoxine, all patients made a full recovery. Of 166 patients with at least 28 day followup, 58 (34.9%) had reappearance of *P. vivax* malaria

between 11 to 65 days or 32.2 (14.4) days following treatment and 11 (6.6%) developed *P. falciparum* malaria 5 to 21 days after vivax treatment. The antimalarial activities (PC_T and PRRs) and treatment success rates (no late appearances of either vivax or *falciparum*) were significantly higher for chloroquine compared with quinine ($p=0.021$) but were similar between artesunate and artemether. The antimalarial activities of mefloquine were similar to halofantrine but the success rate was significantly higher for mefloquine ($p=0.001$). Excluding those receiving artemether and artesunate, patients with vivax reappearance had significantly longer PC_T compared with those with cure (97.2 ± 30.6 vs. 77.5 ± 27.6 hr., $p=0.003$) and the times to vivax reappearance correlated significantly with PC_T, PRR₂₄ and PRR₄₈ ($r\geq0.449$, $p\leq0.007$). These results suggest that vivax malaria in Thailand has developed high grade resistance to pyrimethamine-sulfadoxine. A delayed PC_T of 4 days or more is usually associated with reappearance of vivax at 2-4 weeks after treatment depending on the half life of the given drug. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain and SEAMEO-TROPED Network.

Presented at: Joint International Tropical Medicine Meeting 1999.

COMPARISON OF THE NEUROTOXICITY OF ARTEMISININ DERIVATIVES IN A MOUSE MODEL

**A Nontprasert¹,
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NJ White^{1,3}**

¹ Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

² Laboratoire de Génétique Moléculaire de la Neurotransmission et des Processus Neurodégénératifs, Hôpital de la Pitié Salpêtrière, Paris, France.

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The neurotoxic potential of artemisinin derivatives was investigated in the Swiss albino mouse. Artemether or artesunate in doses ranging between 25 and 250 mg/kg/day were administered daily for 28 days by either intramuscular injection or by the oral route given through direct feeding (once daily) or coated food pellets (continuous oral administration). After starting drug administration, all mice were assessed for behavior, gait, and body weight twice weekly. After completion of the 28 day dosing schedule the mice were assessed weekly for 3 months. Abnormal equilibrium was observed in all groups receiving parenteral artemisinin derivatives at doses > 30 mg/kg/day, ≥ 100 mg/kg/day by oral routes and > 200 mg/kg/day when given in aqueous suspension. The median times to onset of abnormal equilibrium in these groups ranged from 9 to 30 days with no significant differences between the groups. Neurotoxic effects were dose-dependent for both intramuscular and oral routes but there

were marked differences between the drugs. The rate of abnormal equilibrium ranged from 5% of mice receiving oral artesunate 200 mg/kg/day, to more than 95% of mice receiving intramuscular artemether 150 mg/kg/day. Neurotoxicity was significantly more common in the group receiving artemether given intramuscularly or continuously in coated food pellets than in any other group. The results of this study indicate that a prolonged exposure to high doses of either artemether or artesunate results in neurotoxicity in this mouse model and that continuous exposure is considerably more neurotoxic than a once daily brief exposure to high doses. The neurotoxic potential of these antimalarials is determined by their pharmacokinetic properties. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain and SEAMEO-TROPMED Network.

Presented at: Joint International Tropical Medicine Meeting 1999.

RISK FACTORS FOR CHRONIC DISEASES AMONG ROAD SWEEPERS IN BANGKOK

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The nutritional and health status of road sweepers in Bangkok was investigated. Fifty-seven males and 134 females from 10 districts were selected for the study. The districts were sampled as a cluster at random. From each district selected, about 50% of road sweepers volunteered to participate in the investigation. Through questionnaires, the age, marital status, place of origin, drinking and smoking habits were assessed. Anthropometric measurements, blood pressure and lipid profile of these subjects were determined. According to a physical check-up and X-rays, all individuals investigated were apparently healthy. The age of the study group varied between 26 and 57 years. The median for the males was 47 years and for the females 37.5 years. Almost all the road sweepers were married. Smoking and alcohol drinking were widespread. Over- and under-nutrition was found among the group investigated. 26.3% of the males and 1.5% of the females were under-nourished. According to

their systolic values, 15.8% of the males and 6.7% of the females were suffering from hypertension, and 38.6% of the males and 15.7% of the females had hypertension according to their diastolic values. 58.2% of the females and 29.3% of the males were over-nourished. 57.9% of the males and 59.7% of the females had cholesterol levels above 200 mg/dl. Pathological values of LDL cholesterol were determined in 26.3% of the males and 28.4% of the females. The habit of consuming tonic drinks was widespread among the workers. The study concluded that behavior risk factors are highly prevalent in this group of workers belonging to the lower socio-economic class. Further investigations are presently being undertaken to study the after-effects of air pollution among this group of workers. The results will be reported in future publications. ■

Published in: Southeast Asian J Med Public Health 1997;28(1):36-45.

THIAMINE DEFICIENCY AND MALARIA IN ADULTS FROM SOUTHEAST ASIA

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Background: Thiamine deficiency (beriberi) is common in some parts of southeast Asia. Acute thiamine deficiency can mimic many complications of malaria, such as encephalopathy and lactic acidosis. We examined the incidence of thiamine deficiency in adults admitted to hospital with malaria in Thailand.

Methods: For this prospective study, we recruited consecutive patients with malaria or other febrile illness who presented to Paholpolpayuhasena Hospital, Kanchanaburi Thailand, between May and July, 1992. We used the activation coefficient (α) for transketolase activity in erythrocytes to measure thiamine deficiency (defined as $\alpha > 1.31$) in patients with severe and uncomplicated

malaria and in controls (patients' relatives and healthy volunteers). To exclude the possibility of interference in the assays, transketolase activity was also measured in erythrocytes used to culture parasites.

Findings: 12 (52%) of 23 patients with severe malaria and 10 (19%) of 54 patients with uncomplicated malaria had a values above the normal range ($p < 0.0001$ and $p = 0.0014$, respectively, compared with controls), which indicated severe thiamine deficiency. Thiamine deficiency was more severe in patients with cerebral malaria than in those with uncomplicated malaria and the controls ($p = 0.008$).

Interpretation: In adults admitted to hospital in Thailand, thiamine deficiency commonly complicates acute falciparum malaria, particularly in severe infections, and could contribute to dysfunction of the central nervous system. ■

Published in: *Lancet* 1999;353:546-9.

LEAD EXPOSURE, URINARY δ -AMINOLEVULINIC ACID CONCENTRATIONS AND HAEMATOLOGICAL PARAMETERS OF ROAD SWEEPERS WORKING IN CONGESTED AREAS OF BANGKOK

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Road sweepers are especially exposed to environmental pollution. This study investigates the lead exposure, urinary δ -aminolevulinic acid concentration (ALA) and haematological parameters of road sweepers working in traffic-congested areas of Bangkok. One hundred and ninety-four apparently healthy road sweepers aged 20-59 years were investigated. One hundred and thirty-nine staff from an academic institution served as controls. Both male and female road sweepers had slightly, but significantly, lower mean corpuscular haemoglobin concentration (MCHC) values. The white blood cell count (WBC) in female road sweepers was significantly higher compared with the female controls. The proportion of reticulocytes was higher in male and female road sweepers compared with the controls, while no difference was found in blood lead levels and ALA between male road sweepers and controls. Female road sweepers had slightly higher blood lead levels compared with the controls. ALA was no different between both groups of females. The proportion of road sweepers with basophilic stippling was more than double in comparison with the controls; contrary to expectations, obvious signs and symptoms of lead poisoning were not evident in the group of road sweepers. There are, however, more discrete indications that working in this heavily polluted environment is not without health risks. ■

Published in: *J Nutr & Environ Med* 1999;9:109-14.

A CLINICAL TRIAL OF COMBINATION OF ARTESUNATE AND MEFLOQUINE IN THE TREATMENT OF ACUTE UNCOMPLICATED FALCIPARUM MALARIA: A SHORT AND PRACTICAL REGIMEN

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The difficulties in treating drug-resistant falciparum malaria in Thailand are compounded by the necessity of giving antimalarials over long periods of time. The resultant fall in patient compliance not only lowers cure rates but also predisposes to the further spread of drug-resistance. Sequential treatment with artesunate given over 5 days followed by mefloquine produced 100% cure rates in a previous study, but might not be a suitable regimen for field treatment. We conducted a clinical trial of a combination of artesunate and mefloquine given twice daily for 2 days in 150 patients with acute uncomplicated falciparum malaria. The dose of artesunate (200 mg) and mefloquine (312.5 mg) was given simultaneously in a separate package. All patients were admitted to hospital in Bangkok for 28 days to exclude re-infection and monitor the possible adverse effects. One hundred and thirty patients completed the study with 28 days follow-up. Twenty patients (13%) left the hospital prior to completion of follow-up for reasons unrelated to their treatment. Cure rate was 97% (126/130). There were no RII or RIII failures and all four patients with treatment failures were of the RI type. The mean parasite clearance time and fever clearance time were 46.4 and 42.5 hours respectively. All patients

tolerated the combination of drugs well and there were no serious toxic adverse reactions. The results indicate that a combination of artesunate and mefloquine given twice daily for 2 days is effective and well-tolerated in patients with acute, uncomplicated falciparum malaria and suitable as an alternative treatment for multidrug resistant falciparum malaria. ■

Published in: Southeast Asian J Trop Med Public Health 1999 (in press).

THE RATIONAL USE OF QINGHAOSU AND ITS DERIVATIVES: WHAT IS THE FUTURE OF NEW COMPOUNDS?

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Artesunate and artemether are the most effective preparations used for treatment of severe and multidrug resistant falciparum malaria. However, their availability (supply) and licensing difficulties are the major limitations to their use worldwide.

At the Bangkok Hospital for Tropical Diseases, we have studied new preparations of artemisinin derivatives (dihydroartemisinin, arteether, and artesunate suppository) as a single drug or in combination with mefloquine. The

results revealed that the three preparations used alone or in combination with mefloquine are safe, well tolerated and efficacious for treatment of multidrug resistant falciparum malaria both in uncomplicated and complicated cases, and severe falciparum malaria. These clinical trials have been published in international journals for tropical diseases. These preparations have been licensed for use in some countries and are being applied for registration in various countries worldwide. ■

Published in: Médecine Tropicale 1998;58:89-92.

CONTRASTING FUNCTION OF IgG AND IgE ANTI-MALARIA ANTIBODIES IN UNCOMPLICATED OR SEVERE *P. FALCIPARUM* MALARIA

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Plasmodial infection results in a significant elevation of the blood concentrations of immunoglobulins, including IgE. Two well-characterized groups of adult Thai patients with either uncomplicated or severe *P. falciparum* malaria were studied during four weeks. The mean parasitemias were approximately 3x higher in patients with severe, than in those with uncomplicated, disease. The mean concentrations of total IgG and IgG antiplasmodial antibodies were highest in the patients with uncomplicated disease. IgE anti-plasmodial antibodies were present in approximately 65% of the patients and their concentrations were positively correlated to parasitemia. Moreover, the mean concentrations of the IgE antibodies were highest in the patients with severe disease. While these results confirm that IgG anti-plasmodial antibodies are protective in *P. falciparum* malaria, the different distribution of IgE antibodies together with their known capacities to induce local overproduction of TNF suggest that they contribute to the pathogenesis of this infection. ■

Published in: *Am J Trop Med Hyg* 1999 (in press).

ATOVAQUONE AND PROGUANIL HYDROCHLORIDE (MALARONE™) FOR TREATMENT OF MALARIA

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Background: Safe and effective new drugs are needed for the treatment of malaria. Atovaquone and proguanil hydrochloride (Malarone™) is a new antimalarial combination that has recently become available in many countries.

Method: Data were reviewed from clinical trials evaluating atovaquone/proguanil for treatment of malaria.

Results: In ten clinical trials, treatment of uncomplicated falciparum malaria with 1000 mg atovaquone and 400 mg proguanil hydrochloride (or the equivalent based on body weight in patients ≤ 40 kg) once daily for 3 days achieved cure in 514 of 521 (99%) evaluable patients. Treatment-limiting adverse events occurred in <1% of patients (vomiting in four, anaphylaxis in one).

Atovaquone/proguanil has been used to provide radical cure prior to initiation of placebo-controlled trials of malaria prophylaxis. Recurrent parasitemia occurred within 28 days in none of 99 subjects who subsequently received prophylaxis with atovaquone/proguanil and one of 81 subjects who subsequently received a placebo. Atovaquone/proguanil is also effective for treatment of malaria caused by the other three *Plasmodium* species that cause malaria in humans. For treatment of vivax malaria, therapy with primaquine in addition to atovaquone/proguanil is needed to prevent relapse from latent hepatic hypnozoites.

Conclusion: Atovaquone and proguanil hydrochloride is a safe and effective combination for the treatment of malaria. ■

Published in: *J Travel Med* 1999;6(suppl 1):S18-S20.

MALARONE (ATOVAQUONE AND PROGUANIL HYDROCHLORIDE): A REVIEW OF ITS CLINICAL DEVELOPMENT FOR TREATMENT OF MALARIA

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The continuing spread of drug-resistant malaria emphasizes the need for new antimalarial drugs. Atovaquone is a broad-spectrum antiprotozoal drug with a novel mechanism of action, via inhibition of parasite mitochondrial electron transport, and a favorable safety profile. Early studies with atovaquone alone for treatment of malaria demonstrated good initial control of parasitemia but an unacceptable rate of recrudescence parasitemia. Parasites isolated during recrudescence after treatment with atovaquone alone were resistant to atovaquone *in vitro*. The combination of atovaquone and proguanil is synergistic *in vitro*, and clinical studies demonstrated enhanced efficacy of the combination, compared with either drug alone for

treatment of malaria. Malarone[™], a fixed-dose combination of 250 mg atovaquone and 100 mg proguanil hydrochloride, is available in many countries for treatment of acute, uncomplicated malaria caused by *Plasmodium falciparum*. At the recommended dose (in adults, four tablets once daily for 3 days), the overall cure rate was >98% in more than 500 patients with falciparum malaria. In four randomized, controlled clinical trials, treatment with atovaquone and proguanil hydrochloride was significantly more effective than mefloquine (Thailand), amodiaquine (Gabon), chloroquine (Peru and the Philippines) or chloroquine plus pyrimethamine/sulfadoxine (Philippines). In clinical trials where the comparator drug was highly effective, treatment with atovaquone and proguanil hydrochloride was equally effective. Parasites isolated during recrudescence after treatment with the combination of atovaquone and proguanil are generally not resistant to atovaquone *in vitro*. The most commonly reported adverse events in clinical trials (abdominal pain, anorexia, nausea, vomiting, diarrhea and coughing) occurred with similar frequency in patients treated with a comparator drug. Malarone is a safe and effective new agent for the treatment of malaria.

The continuing spread of drug-resistant malaria and a new appreciation of the side effects associated with many existing antimalarial agents have emphasized the need for new drugs for prevention and treatment of malaria. Malarone[™], a fixed-dose combination of atovaquone and proguanil hydrochloride, is the first new antimalarial therapy in more than 40 years originating from industry-sponsored research. This combination is significantly more effective than either component alone, is effective against strains that are resistant to a variety of other antimalarial drugs, and has a favorable safety profile. In the present paper we review the results of clinical studies that have demonstrated the safety and efficacy of atovaquone and proguanil hydrochloride and supported its registration for treatment of malaria. ■

Published in: Am J Trop Med Hyg 1999;60(4):533-41.

GOOD INITIAL THERAPEUTIC RESPONSE OF *PLASMODIUM VIVAX* TO CHLOROQUINE TREATMENT IN THAILAND

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Chloroquine has been the standard treatment for *Plasmodium vivax* for more than 40 years. Recently, several reports have suggested the occurrence of chloroquine-resistant *P. vivax*. We studied 913 subjects with a diagnosis of *P. vivax* prospectively to find out the magnitude of this problem in Thailand. All of them were admitted to the Bangkok Hospital for Tropical Diseases and were randomized for treatment with chloroquine (25 mg base/kg body weight over 3 days) and primaquine 15 mg/day for 14 days orally as a standard treatment for *P. vivax* malaria or chloroquine alone. All the patients with a mean age of 24.6±8.9 years were followed up for 28 days. About two-thirds of the cases were male. Most of the cases studied (82.1%) contracted the malaria infection on the Thai-Myanmar border. 91.2% (833/913) responded well to treatment. 78 cases (8.5%) had a positive asexual form of *P. falciparum* malaria during the follow-up period of 28 days in the hospital and were treated with a standard regimen for *P. falciparum* infection. There were only two cases (0.2%) who had a reappearance of asexual *P. vivax* on day 14 and day 28 with RI pattern. The chloroquine-resistant cases were re-treated with the same regimen with a good outcome. The mean parasite clearance time (PCT) and fever clearance time (FCT) were 60.6±20.6 and 29.2±25.9 hours respectively. There was no significant difference ($P>0.05$) in PCT, FCT, G6PD status and history of previous malaria infection between chloroquine resistant and sensitive patients. Both groups of treatment (chloroquine alone and chloroquine followed by primaquine) were compared in

respect of cure rate, PCT, FCT, and RI response. There was no significant difference ($p>0.05$). There was no mortality in our studied patients.

We concluded that chloroquine-resistant *P. vivax* is rare in Thailand, and most *P. vivax* remain sensitive and respond well to chloroquine. ■

The study was supported by the Wellcome Trust, Oxford Tropical Medicine Research Programme, 183 Euston Road London NW1 2BE, UK.

Published in: Ann Trop Med Parasitol 1999 (in press).

CONSENSUS RECOMMENDATION ON THE TREATMENT OF MALARIA IN SOUTHEAST ASIA

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Southeast Asia harbors the most drug-resistant malaria parasites in the world. Antimalarial treatment recommendations in recent years have had to undergo a series of changes to accommodate worsening resistance. The situation is particularly critical on the eastern and western borders of Thailand where *Plasmodium falciparum* has developed resistance to chloroquine, sulphadoxine-pyrimethamine, and now in recent years, mefloquine. A closed meeting of regional and international experts was held on 27 August 1997 to review recent information on treatment responses, and provide evidence-based recommendations for treatment. The consensus recommendation on the treatment of malaria in Southeast Asia will help and guide physicians on how to manage a patient who has contracted malaria in Southeast Asia where the most multidrug resistant falciparum malaria in the world is harbored. ■

The study was supported by the Wellcome Trust, Oxford Tropical Medicine Research Programme, 183 Euston Road London NW1 2BE, UK.

Published in: Southeast Asian J Trop Med Public Health 1998;29(2):355-60.

RESEARCH ON NEW ANTIMALARIAL DRUGS AND THE USE OF DRUGS IN COMBINATION AT THE BANGKOK HOSPITAL FOR TROPICAL DISEASES

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With the emergence of multidrug resistant falciparum malaria in Thailand, various approaches have been taken. Research on new antimalarial drugs and the use of existing available drugs with modification are urgently needed. New drugs and drugs in combination such as pyronaridine, WR 238605, arteether, dihydroartemisinin, benflumetol atovaquone/proguanil are being evaluated. Recommended drug combinations for the treatment of patients suffering from uncomplicated falciparum malaria include quinine-tetracycline for 7 days, or sequential treatment of artesunate (600 mg given over 5 days) followed by mefloquine (1,250 mg divided into 2 doses 6 hours apart). Sequential treatment is highly recommended for those who have failed other treatment regimens. Other combinations, such as a short course sequential treatment of artesunate (300 mg given over 2.5 days) followed by a single dose of 750 mg mefloquine, or a combination of mefloquine 1,250 mg

together with tetracycline 1 g per day or doxycycline 200 mg per day for 7 days are alternative treatment regimens with acceptable cure rates. The simultaneous administration of artesunate and mefloquine, in various doses and durations of treatment, is currently being investigated. Until proven otherwise, the drug combinations are still recommended for all adult patients suffering from acute uncomplicated falciparum malaria contracted in multidrug resistant areas. In severe malaria and malaria in children, the drug combinations need further investigation. ■

Published in: Southeast Asian J Trop Med Public Health 1998;29(2):344-54.

INCIDENCE OF FILARIASIS AS A CO-INFECTION IN MALARIA PATIENTS COMING FROM THAI-MYANMAR BORDER BETWEEN 1995-1997

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Concomitant infection with malaria and filariasis has been reported in animals and studies about the influence of co-infection on the severity of malaria have been conducted. So we studied the prevalence and severity of co-infections. We prospectively studied 4,201 malaria patients admitted to the Bangkok Hospital for Tropical Diseases, Mahidol University, Thailand from 1995-1997. We found only 8 cases (0.2%) of the total malaria inpatients with microfilaria in their blood smear. All of them were *W. bancrofti* and most of them were uncomplicated malaria infections. Only one patient had cerebral malaria, which was cured after treatment without complication. All filarial infected patients were asymptomatic and cured with diethylcarbamazine. All patients with co-infection of malaria and filariasis had resided in the Thai-Myanmar border area, known as an endemic area for both diseases. So the existence of co-infection with malaria and filariasis was confirmed in Thailand especially in the group of patients coming from the Thai-Myanmar border. ■

Published in: Jpn J Trop Med Hyg 1998;26(4):323-6.

A COMPARISON OF THREE DIFFERENT DIHYDROARTEMISININ FORMULATIONS FOR THE TREATMENT OF ACUTE UNCOMPLICATED FALCIPARUM MALARIA IN THAILAND

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We compared the safety and efficacy of three formulations of dihydroartemisinin for the treatment of acute uncomplicated falciparum malaria in patients who received a total dose of 600 mg dihydroartemisinin over 5 days. The first group was treated with dihydroartemisinin produced and formulated in the People's Republic of China. The second group was treated with dihydroartemisinin produced in Vietnam but formulated by the Government Pharmaceutical Organization of Thailand. The third group was treated with dihydroartemisinin produced and formulated by the Government Pharmaceutical Organization of Thailand. All patients were admitted to hospital to evaluate safety and efficacy for a total of 28 days. By the third day of treatment, most patients were blood-smear negative for parasites and none had serious adverse effects. Minor symptoms such as nausea, dizziness and headache were similar in the three groups and disappeared after 3 days of treatment. One-hundred and thirty-three patients completed the 28-day

follow-up period. The cure rates of groups I, II and III were 80%, 85%, and 92%, respectively ($P > 0.02$). There were no significant differences in fever clearance or parasite clearance among the three groups. We concluded that the three formulations of dihydroartemisinin produced and formulated in different countries were safe and effective in treating uncomplicated falciparum malaria acquired in Thailand. ■

Published in: Int J Parasitol 1998;28(8):1213-8.

GASTRIC INTRAMUCOSAL pH AS A PROGNOSTIC INDEX OF MORTALITY IN CEREBRAL MALARIA

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To determine if measurements of gastric intramucosal pH have prognosis implications regarding ICU mortality, 42 cerebral malaria patients in ICU were studied. Gastric intramucosal pH was measured on ICU admission and again 6 hours later. A value of >7.30 was used to differentiate between normal and low gastric intramucosal pH. 32 patients had a normal gastric intramucosal pH and 10 patients had a low gastric intramucosal pH on ICU admission. The mortality rate was greater in the low gastric intramucosal pH group on admission (40% v. 0%; $P < .05$). Apart from coma, the presence of malarial complications was similar in the low and normal gastric intramucosal pH groups. Further stratification of patients according to gastric intramucosal pH measured 6 hours after admission showed a greater

mortality rate in patients with persistently low gastric intramucosal pH compared with patients with normal gastric intramucosal pH during the first 6 hours (57.14% v. 0%, $P < .05$). Measurement of gastric intramucosal pH on ICU admission, and again 6 hours later, has a high specificity for predicting survival in this ICU patient population (84.20% v. 100%). Furthermore, given its relative noninvasive procedure, measurement of gastric intramucosal pH may be a useful addition to monitoring cerebral malaria patients in the ICU. ■

Published in: J Trop Med Parasitol 1999 (in press).

ARTEMISININ DERIVATIVES IN THE TREATMENT OF FALCIPARUM MALARIA IN PREGNANCY

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An artemisinin derivative (artesunate or artemether) was used for the treatment of multi-drug resistant *P. falciparum* malaria in 83 pregnant Karen women; 55 women were treated for a recrudescence following quinine or mefloquine, 12 for uncomplicated hyperparasitaemia episode, and 16 had not declared their pregnancy when treated. The women were followed weekly until delivery. Artesunate and artemether were well tolerated and there were no drug-related adverse effects. Recrudescences within 42 days occurred in 16% of the treated episodes. Overall 73 (88%) of pregnancies resulted in live births, 3 (4%) in abortion and 2 (3%) in stillbirth, and 5 women were lost to follow-up before delivery. There were no congenital abnormalities in any of the newborns, and the 46 children, followed for more than 1 year, all developed normally. These preliminary findings on the use of artemisinin derivatives in pregnancy are reassuring. ■

The study was supported by the Wellcome Trust, Oxford Tropical Medicine Research Programme, 183 Euston Road London NW1 2BE, UK.

Submitted to: Trans Roy Soc Trop Med Hyg 1999.

ARTESUNATE AND MEFLOQUINE IN THE TREATMENT OF UNCOMPLICATED MULTI-DRUG RESISTANT HYPERPARASITAEMIC FALCIPARUM MALARIA

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Oral artesunate is the most effective treatment for uncomplicated hyperparasitaemia in falciparum malaria. To assess the contribution of mefloquine to therapeutic efficacy in an area endemic for mefloquine resistant *P. falciparum*, an open randomised comparison of a 5-day course of oral artesunate (total dose: 12 mg/kg) with and without mefloquine (25 base mg/kg) in uncomplicated hyperparasitaemia (> 4% parasitised red blood cells) was conducted in 100 adults and children. Both regimens were well tolerated and gave equally rapid clinical responses (within 48 hours 84% of patients were aparasitaemic and 96% were afebrile), but the recrudescence rate assessed at day 42 was 6% in those receiving artesunate with mefloquine, compared with 36% in those receiving artesunate alone (Adjusted hazards ratio 7 [95% Confidence Interval: 2 to 32%]; $p < 0.0001$). In addition the efficacy of a 7-day course of artesunate, with and without the addition

of mefloquine, was monitored in 178 patients who were not part of the randomised comparison. The failure rate was also lower in those receiving artesunate and mefloquine; 7% [95% CI: 2 to 13%] compared with 26% [95% CI: 8 to 44%] in patients treated with artesunate alone. An oral regimen of 5 or more days of artesunate, together with mefloquine (25 mg/kg) given on day 2, is an effective treatment for uncomplicated hyperparasitaemic falciparum malaria in this area of high level multi-drug resistance. ■

The study was supported by the Wellcome Trust, Oxford Tropical Medicine Research Programme, 183 Euston Road London NW1 2BE, UK.

Published in: *Trans R Soc Trop Med Hyg* 1998;92:207-11.

CLINICAL USE OF ARTEMISININ AND ITS DERIVATIVES IN THE TREATMENT OF MALARIA

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Malaria is one of the world's most important tropical diseases, causing great human suffering and loss of life in the affected countries. There are four species of Plasmodia causing human malaria: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. Of the four species of Plasmodia, it is *P. falciparum* which causes the greatest problem. Mosquito control is often not cost-effective in areas where

the disease is most severe and where transmission interruption cannot be sustained. Therefore, current malaria control places emphasis on early diagnosis, treatment with effective antimalarials, and selective use of preventive measures including vector control where they can be sustained. The treatment of malaria has changed over the past two decades in response to declining drug sensitivity in *P. falciparum* and a resurgence of the disease in tropical areas. Some other problems are increasing numbers of severe and cerebral malaria cases, the high cost of drugs, side effects, and the need for multiple dose regimens. Although chloroquine was recently the drug of choice in Africa, resistance has now spread to all major malarial-endemic areas. For multidrug resistant *P. falciparum* malaria, the choice of treatment is mefloquine, halofantrine, or quinine plus tetracycline. After mefloquine became the drug of choice in some Southeast Asian countries, *P. falciparum* malaria, resistant to mefloquine, developed. The alternative treatment with oral quinine or quinidine is not well-tolerated. Although the combination of quinine with tetracycline or doxycycline remains more than 85 percent effective nearly everywhere, compliance with seven-day courses of treatment required for resistant *P. falciparum* infections is poor. The second-line drug, a combination of a long-acting sulfonamide (usually sulfadoxine) and pyrimethamine carries a risk of severe side effects and is facing growing resistance. ■

Published in: *Artemisia*. Wright C. (ed.), UK. 1999 (in press).

CGP 56697 VERSUS MEFLOQUINE FOR TREATMENT OF *P. FALCIPARUM* MALARIA

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Background: Multi-drug resistant *P. falciparum* malaria poses an increasing threat in South East Asia. The age-old Chinese herbal remedy artemisinin (qinghaosu) has proved effective against multi-drug resistant malaria, but when used alone is associated with a high rate of recrudescence. CGP 56697, a combination therapy of two antimalarials: the artemisinin derivative artemether and benflumetol, a novel antimalarial also developed in China, has a reported low recrudescence rate and is compared in efficacy with mefloquine.

Method: A randomised, double-blind trial with 252 patients, aged 13-63 years (median 22), treated either with CGP 56697 (4 x 4 tablets each containing 20 mg artemether and 120 mg benflumetol, given at 0, 8, 24 and 48 hours; total 320 mg artemether, 1,920 mg benflumetol), or with mefloquine (3 x 250 mg at 0 hr, 2 x 250 mg at 8 hrs; total 1,250 mg). Patients were kept as hospital in-patients outside the transmission area to prevent re-infection during the trial. Progress and possible adverse effects were monitored by blood film parasitology, temperature, ECG, routine blood and urine analysis.

Findings: The 28-day cure rate with CGP 56697 was lower than with mefloquine (M): C, 69.3%; M, 82.4% (p=0.02). However, CGP 56697 was more effective than mefloquine in a) parasite clearance time (C, 43 hrs; M, 66 hrs, p<0.001), b) fever clearance time (C, 32 hrs; M, 54 hrs, p<0.005), and c) gametocyte clearance (C, 152 hrs; M, 331 hrs, p<0.001).

Interpretation: CGP 56697 is an effective antimalarial, active against falciparum malaria resistant to other drugs. Compared to mefloquine, it is markedly superior in parasite clearance and fever reduction rates, but inferior in terms of 28-day cure rate at this dosage. Its powerful anti-gametocyte activity may help reduce malaria transmission. ■

Published in: *Am J Trop Med Hyg* 1999 (in press).

EFFICACY OF SIX DOSES OF ARTEMETHER-BENFLUMETOL IN THE TREATMENT OF MULTI-DRUG RESISTANT *FALCIPARUM* MALARIA

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The new oral fixed combination artemether-benflumetol (CGP 56697) has proved an effective and well-tolerated treatment of multi-drug resistant falciparum malaria, although cure rates using the four dose regimen have been lower than with the currently recommended alternative; artesunate-mefloquine. Two six-dose schedules (total adult dose 480 mg artemether and 2,880 mg of benflumetol) were therefore compared with the previously used four-dose regimen (320 mg artemether and 1,920 mg of benflumetol) in a double-blind trial involving 359 patients with uncomplicated multi-drug resistant falciparum malaria. There were no differences between the three treatment groups in parasite and fever clearance times, and reported adverse effects. The two six-dose regimens gave 96.9% and 99.1% adjusted 28 day cure rates respectively, compared to 83.3% for the four-dose regimen (P < 0.001). These six-dose regimens of artemether-benflumetol provide a highly effective and very well

tolerated treatment for multidrug resistant falciparum malaria. ■

The study was supported by the Wellcome Trust, Oxford Tropical Medicine Research Programme, 183 Euston Road London NW1 2BE, UK.

Published in: *Am J Trop Med Hyg* 1999;60(6):936-42.

EFFICACY OF PRIMAQUINE REGIMENS FOR PRIMAQUINE-RESISTANT *PLASMODIUM VIVAX* MALARIA IN THAILAND

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To define the current efficacy of Fansidar® (F. Hoffmann-La Roche Ltd., Basel Switzerland) (pyrimethamine and sulfadoxine), primaquine in a high dose, and artesunate for treating acute *Plasmodium vivax* malaria, we conducted a comparative clinical trial of these 3 drugs in an open-label study. Patients (15-65 years old) were assigned to 1 of 4 treatment regimens in a serial order. Ninety percent of the patients were infected at the Thailand-Myanmar border. Patients in Group I (n = 23) received Fansidar® (3 tablets, 75mg of pyrimethamine and 1,500 mg of sulfadoxine, a single dose on the first day), Group II (n = 23) received Fansidar® (3 tablets, 75 mg of pyrimethamine and 1,500 mg of sulfadoxine, a single dose on the first day) and then received primaquine (30 mg a day for 14 days), Group III (n = 23) received primaquine (30 mg a day for 14 days), and Group IV (n = 23) received artesunate (200 mg once a day for 3 days) and then primaquine (30 mg a day for 14 days). Cure rates on day 28 of follow-up were 40%, 100%, 100% and 100% in Group I, II, III, and IV, respectively. There were 4 and 5 patients in Group I showing post-treatment reappearance of parasitemia at ≤ 16 days and between 17 and 28 days, respectively. Patients in the other 3 Groups showed negative parasitemias within 7 days after treatment. Artesunate plus primaquine (Group IV) cleared parasitemia faster than the other 3 regimens. There is a high proportion of ineffectiveness of Fansidar® for treatment of *P. vivax* malaria and it should no longer be used for treatment of *P. vivax* malaria acquired at the Thailand-Myanmar border. A high dose of primaquine is safe and effective in the treatment of *P. vivax* malaria during the 28-day follow-up period. ■

Published in: *Am J Trop Med Hyg*: 2000;62(3), (in press).

MANAGEMENT OF MALARIA WITH ACUTE RENAL FAILURE

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Acute renal failure (ARF) is one of the three most common causes of death in severe malaria. The outcome depends on the time between onset of symptoms and arrival at a health facility, and on the available facility resources and health worker capacity to manage the complications. Most severely ill patients live in rural areas endemic for malaria where the facilities are limited.

Before 1980, the mortality rate of patients with severe complicated malaria was 29-50%. Moreover, in cases with lung complications, the mortality rate rose to 60-75%. During the Vietnam War the mortality from ARF fell from 50% to 15-20% once dialysis facilities became available. Since 1980, with early dialysis for renal failure and full respiratory support, the mortality rate of complicated malaria has declined to 10-20%. In Vietnam, the mortality of ARF with malaria has fallen from 75% to 26% with the introduction of peritoneal dialysis.

In our own study of 122 patients with malarial acute renal failure admitted to the Bangkok Hospital for Tropical Diseases, during the period 1991-1997, 101 (90.2%) patients received hemodialysis. Ninety-three patients were oliguric and the remainder were non-oliguric. The overall mortality was 11%. Of the 12 patients who died, 11 were jaundiced and 8 had cerebral malaria. ■

Published in: *Afr J Nephrol* 1999;3:67-72.

DETERMINATION OF *PLASMODIUM FALCIPARUM* TREATMENT FAILURE USING PCR-SINGLE-STAND CONFORMATIONAL POLYMORPHISM

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The inability to distinguish *Plasmodium falciparum* treatment failures from new infections is an important impediment to the evaluation of antimalarial drugs. Based on a pilot study utilizing PCR-single-stand conformational polymorphism (SSCP) analysis to genotype *P. falciparum* isolates, we sought to confirm that PCR-SSCP could reliably distinguish treatment failures from unrelated infections with a sample size adequate to estimate the accuracy of this technique. PCR-SSCP analysis was performed on 36 paired isolates collected from individuals who failed treatment in Thailand. In every case (36 of 36, 100% [95% CI 90-100%]), the PCR-SSCP pattern of the recrudescence isolates matched, or was contained within, the pattern of the primary isolate. We assessed the ability of PCR-SSCP to separate unrelated

infections by comparing each recrudescence isolate to each of the unrelated primary isolates. Of 1260 comparisons, 1258 had unique PCR-SSCP patterns (99.8% [95% CI 99.4-100%]). The results indicate that PCR-SSCP can be used to differentiate *P. falciparum* treatment failures from re-infections. ■

Published in: *Clin Inf Dis* 1999 (in press).

SEROLOGICAL EVALUATION OF MALARIA PATIENTS IN THAILAND; ANTIBODY RESPONSE AGAINST ELECTROPHORESED ANTIGENIC POLYPEPTIDES OF *PLASMODIUM FALCIPARUM*

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It was reported that a 47kDa antigenic polypeptide of *Plasmodium falciparum* had been strongly presented in the sera from 1) imported Japanese malaria patients with severe symptoms and 2) symptomatic and parasitemic inhabitants in endemic areas in the Sudan, Malaysia and the Philippines. In the present study, we observed the reactivity of the sera from falciparum malaria patients who had been hospitalized in the Bangkok Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, and compared the antibody response against the 47kDa antigenic polypeptide according to the severity of the patients. It was observed that antibodies to this molecule were more commonly shared in sera from more severe patients, although the IFAT titers against the whole *P. falciparum* parasite antigen were lower in the group, which suggested that this antibody against the 47kDa

molecule was playing a specific role at a severe stage of the infection. Determination of the immunological features of the antigenic molecules of parasites by this type of sero-epidemiological study will provide a new assay system for evaluation of immune status of individuals in different severity and suggest a way of vaccine development- ■

Published in: *Southeast Asian J Trop Med Public Health* 1998;29(2):341-3.

SEROLOGICAL EVALUATION OF MALARIA PATIENTS IN THAILAND, WITH PARTICULAR REFERENCE TO THE REACTIVITY AGAINST A 47kD ANTIGENIC POLYPEPTIDE OF *PLASMODIUM FALCIPARUM*

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Quite a few antigenic polypeptides of *Plasmodium falciparum* (*P.f.*) have been investigated for their potential to serve as vaccine. Applying SDS-PAGE and Western blotting technique, we have also studied an antigenic polypeptide, a relative molecular mass of 47kD, which may be related to the development of a protective immune response in the host.

First, the 47kD was subjected to molecular characterization. Preparatively electrophoresed *P.f.* antigen was blotted onto the PVDF membrane and the 47kD band was cut off from the membrane. The polypeptide was eluted, treated with lysyl-end proteinase, subjected to reversed phase chromatography, and blotted again on PVDF membrane by micro blotter. The chromatogram showed that several fractions of the 47kD polypeptides were

obtained and small pieces of membrane were cut according to the respective peak and subjected to the peptide sequencer. The sequencing of the peak molecules revealed that obtained amino acid sequences were parts of *P.f.* enolase. This enolase is a key enzyme of the glycolytic pathway and catalyzes the conversion of 2-phosphoglycerate to phosphoenol pyruvate, which is the ninth reaction of the eleven-step pathway from glucose to lactic acid, and the only dehydration reaction in this series. The degree of identity of the *P.f.* enolase to that from the human host is 68.4%, so that the enolase would not be a favorable target for chemotherapeutic intervention because of the relatively higher identity. Katakai's analysis based on the standard Chou-Fasman method proved only a helices and did not give reliable $\beta+\alpha$ -Sheet predictions, however, the similarity to the 8-fold $\beta+\alpha$ -Barrel structure as determined by that of yeast can be predicted.

Although it is not clear if immunity of the host can be established by the antibody binding to the antigen, consequently inhibiting glycolysis of the parasite, so that we have raised a monoclonal antibody against the 47kD antigenic molecule and investigated some of the potentiality of the molecule *in vitro*. Optical section images of the confocal micrograph of the IFAT demonstrated that this monoclonal antibody reacted specifically at the schizont stage of the parasite. Incubation of the monoclonal antibody with the synchronized erythrocytic forms of *P.f.* for 30 hours *in vitro*, inhibited the maturation of the schizonts in a dose dependent manner. Also, cultivation of the asynchronous parasites with the monoclonal antibody inhibited the growth rate of the parasites. Therefore, the determination of the active site of the *P.f.* enolase and neutralization or inhibition of enolase activity will be of great importance. It is known that parasitized erythrocytes increase their utilization of glucose as much as 100 times, and the rate of uninfected host red cells, and consequently make the host hypoglycemic. Inhibition of this enzymatic activity could also contribute to the betterment of the host's symptoms.

It has already been proven that this 47kD antigenic polypeptide of *P.f.* had been strongly presented in the sera from 1) imported Japanese malaria patients with severe symptoms and 2) symptomatic and parasitemic inhabitants in endemic areas in the Sudan, Malaysia and the Philippines. We also studied the reactivity of the sera from malaria patients who had been hospitalized in the Faculty of Tropical Medicine, Mahidol University, Thailand. We also compared the reactivity of the sera according to the severity of the patients suffering from *P.f.* malaria, of which the results are shown in this study. The fact that specific antibodies to this molecule were commonly found in sera from acute patients and humans in endemic areas suggested that they may play a certain role at an acute stage of infection. ■

Published in: *Tokai J Exp Clin Med* 1998;23(2):97-8.

APPLICATION OF GENETIC MARKERS TO THE IDENTIFICATION OF RECRUDESCENT *PLASMODIUM FALCIPARUM* INFECTIONS ON THE NORTH WESTERN BORDER OF THAILAND

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Parasite genotyping by polymerase chain reaction (PCR) was used to distinguish recrudescence from newly acquired *Plasmodium falciparum* infections in a Karen population resident on the north western border of Thailand where malaria transmission is low (= 1 infection/person/year). *P. falciparum* infections were genotyped for allelic variation in three polymorphic antigen loci, merozoite surface proteins 1 and 2 (MSP-1 & MSP-2) and glutamate rich protein (GLURP), before and after antimalarial drug treatment. Population genotype frequencies were measured providing the baseline information to calculate the probability of a new infection with a different, or the same, genotype to the initial pre-treatment isolate. Overall, 38% of infections detected following treatment had an identical genotype before, and up to 121 days after, treatment. These post-treatment

genotypes were considered recrudescence because of the low (<5%) probability of repeated occurrence by chance in the same patient. This approach allows studies of antimalarial drug treatment to be conducted in areas of low transmission, as recrudescence can be distinguished confidently from newly acquired infections. ■

Published in: *Am J Trop Med Hyg* 1999;60(1):14-21.

EOSINOPHILIC RESPONSE AND HEMATOLOGIC RECOVERY AFTER TREATMENT FOR *PLASMODIUM FALCIPARUM* MALARIA

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To examine a possible relationship between the T-helper cell type 2 (Th-2) immune response and hematologic recovery after acute falciparum malaria, we followed peripheral blood eosinophil counts and hemoglobin concentrations for four weeks after starting effective treatment in 16 adult Thai patients whose stools were negative for ova and parasites. Eosinophils are induced by Th-2 cytokines and reflect the activity of this arm of the immune response. Eosinophil counts were normal in all but one subject at presentation, probably reflecting predominance of the Th-1 response over the Th-2 response early in the infection, but were elevated in all but one subject by day 7. Eosinophil counts then decreased markedly by day 14 and did not change significantly thereafter. A significant positive correlation was found between peak eosinophil counts on day 7 and the hemoglobin concentration on day 28 ($r = 0.65$, $P = 0.006$).

These results suggest that a robust Th-2 immune response shortly after completing antimalarial therapy predicts for a good recovery from malaria-associated anemia. ■

Published in: *Trop Med Internat Health* 1999 (in press).

INFLUENCE OF HEMOGLOBIN E TRAIT ON THE SEVERITY OF FALCIPARUM MALARIA

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To determine if hemoglobin E trait influences the course of acute malaria, adult patients hospitalized for the treatment of symptomatic infection with *Plasmodium falciparum* were studied retrospectively. Forty-two patients with hemoglobin E trait were compared with 175 reference subjects who did not have hemoglobin E, β -thalassemia, glucose-6-phosphate dehydrogenase deficiency, or β -thalassemia. One patient with hemoglobin E trait (2.4%) had a severe complication of malaria by World Health Organization criteria (cerebral malaria) while 32 subjects in the reference group (18.3%) had one or more severe complications: cerebral malaria (n=18), hyperparasitemia (n=16), renal failure (n=10), severe anemia (n=1) (P=0.044 after adjustment for ethnic categories). The estimated odds of severe complications in the reference subjects were 6.9 times the odds in patients

with hemoglobin E trait (95% confidence interval of 1.2 to 146.4). These results suggest that hemoglobin E trait may ameliorate the course of acute falciparum malaria. ■

Published in: *J Inf Dis* 1999;178:283-6.

THE OCCURRENCE OF POINT MUTATIONS IN THE DIHYDROFOLATE REDUCTASE-THYMIDYLATE SYNTHASE (DHFR) IN THAI ISOLATE OF *PLASMODIUM FALCIPARUM*

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Point mutations at codon 108 in the dihydrofolate reductase-thymidylate synthase (DHFR) gene of *Plasmodium falciparum* resulting in Ser-108→Thr-108 and Ser-108→Asn 108 changes have been reported to be associated with resistance to cycloguanil and pyrimethamine respectively. Polymerase chain reaction (PCR) with specific primers was used to study these point mutations in 38 *P. falciparum* isolates from Thai patients. It was found that the Ser-108 marker was not commonly present with only 1 isolate (2.6%) having it. DNA sequence

variation may be present in Thai isolates as one isolate with high parasitemia was negative in the PCR and another had a shorter PCR product compared to the reported 337 bp size for Ser-108. The Asn-108 marker appeared to occur more frequently (31.6%) than the Thr-108 marker (10.5%) while a large number of these isolates were heterogeneous having both the Ser-108 and Asn-108 (18.4%) or Asn-108 and Thr-108 (31.6%) markers indicating mixed populations of parasites in the same individual. From this study, it appears that Thr-108 and Asn-108 should not be used as the only markers to determine parasite response to cycloguanil and pyrimethamine in Thai isolates, as variant forms and heterogeneity may exist to complicate the diagnosis. ■

Published in: *Southeast Asian J Trop Med Public Health* 1998;29(3):525-8.

POLYCLONAL ANTI-TUMOUR NECROTIC FACTOR- α FAB USED AS AN ANCILLARY TREATMENT IN SEVERE MALARIA

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Single doses (250, 500, 1000 or 2000 units/kg) of an ovine polyclonal specific Fab fragment directed against tumor necrosis factors were given to 17 adult patients with severe falciparum malaria immediately before treatment with artesunate in a pilot study to assess safety and optimal dosage with a view to future studies. Clinical and laboratory variables were compared with 11 controls. In the groups given Fab, there was a tendency for a faster resolution of clinical manifestations and reduction of fever but also a tendency towards longer parasite clearance times. Adverse events were more common in the control group and no early anaphylactoid or late serum sickness reactions occurred in the Fab treated patients. On admission all patients had markedly elevated TNF α (85-1,532 ng/L) and IL-6 concentrations (30-27,500 ng/L), most had elevated IFN γ values and a few had raised IL-2, IL-8 and IL-1 β levels. Antibody treatment reduced IFN γ concentrations in a dose-related manner, but had no obvious effects on levels of other cytokines in this small study, although unbound TNF α was undetectable after Fab treatment. Circulating concentrations of soluble E-selectin, ICAM-1 and VCAM-1 were not affected by Fab treatment. The Fab exhibited two compartment, dose proportional kinetics with an average elimination half-life of 12.0 hr and with about 20% being excreted renally. These results encourage a randomized, placebo-controlled trial in patients with cerebral malaria and provide some guidance about dosage. ■

Published in: Am J Trop Med Hyg 1999;61(1):26-33.

IgE DEPOSITION IN CEREBRAL MICROVESSELS AND ON PARASITIZED ERYTHROCYTE FROM CEREBRAL MALARIA PATIENTS

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Postmortem cerebral tissues of 21 cerebral malaria cases were obtained in Myanmar and Vietnam. The cerebral tissues were examined by light microscopy and by an immunohistologic method. The cerebral malaria patients were categorized into two groups based on the rate of parasitized erythrocytes (PRBC) sequestration in the cerebral tissues: Group I with high (50% or more) PRBC sequestration and Group II with low (less than 50%) sequestration. Deposition of immunoglobulins, IgE and IgG, and *Plasmodium falciparum* antigens were seen in the cerebral microvessels from all specimens in both groups. All specimens in Group I were also positive for IgE and IgG on PRBC in the cerebral section. The frequency of IgE and IgG deposition ranged from 42% to 100%, respectively. In Group II, all specimens were negative for IgE, but positive for IgG. Thus, our data indicate that the amount of deposition of IgE in cerebral microvessels and on PRBC in the cerebral microvessels, especially PRBC, from cerebral malaria patients correlated well with the degree of PRBC sequestration in that site. As IgE containing immune complexes can induce local overproduction of tumor necrosis factor (TNF), a pathogenic factor in cerebral malaria, IgE may contribute to the pathogenicity of this severe disease. ■

CIRCULATING RECEPTORS ICAM-1, VCAM-1, E-SELECTIN AND CHONDROITIN-4-SULFATE A IMPLICATED IN CYTOADHERENCE IN THE COURSE OF SEVERE *PLASMODIUM FALCIPARUM* MALARIA IN THAILAND

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The kinetic profiles of the circulating receptors were compared in a case control study to determine if they could be considered as predictive markers for the severity of *P. falciparum* malaria. We observed a significant difference between ICAM-1s concentrations in severe malaria cases compared with the uncomplicated cases ($p=0,01$). However, there was a significant increase in CSA concentrations in both groups compared with a control group ($p= 10^{-5}$), without correlation between the plasma level of CSA and the severity of malaria infection. Plasma levels of E-selectin and VCAM-1 were increased in the two groups compared with the corresponding control

groups. Our results suggest that the plasma concentration of ICAM-1 may be considered as a marker for the severity of malaria. ■

SERUM CONCENTRATIONS OF G-CSF IN COMPLICATED *PLASMODIUM FALCIPARUM* MALARIA

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It was the aim of the present study to investigate the time course of G-CSF serum concentrations in patients with complicated *P. falciparum* malaria in comparison with other immunological parameters.

26 patients suffering from complicated *P. falciparum* malaria were included in the study; 20 age- and sex-matched healthy volunteers were used as the negative control group. Serum samples for determination of G-CSF were taken on day 0, 7 and 14. A commercially available ELISA was used for analysis.

Serum concentrations of G-CSF were increased in patients with complicated *P. falciparum* malaria on admission (583 740 pg/ml). Values had decreased to within

the normal range by day 7 (13.3 8.4 pg/ml; control group: 16 13.5 pg/ml). A significant correlation was found between G-CSF (d0) and procalcitonin, the parasite count, erythropoietin and macrophage inflammatory protein-1 alpha serum concentrations.

In conclusion, elevated serum concentrations of G-CSF were found in patients with complicated *P. falciparum* malaria on the day of admission. This might indicate a role of G-CSF in the acute defense mechanism against these parasites. ■

PLASMA LEVELS OF THE IL-6 CYTOKINE FAMILY IN PATIENTS WITH SEVERE *PLASMODIUM FALCIPARUM* MALARIA

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Plasma levels of members of the interleukin-6 (IL-6) family (IL-6, soluble IL-6-receptor, soluble gp130, leukemia inhibitory factor (LIF), and ciliary neurotrophic factor (CNTF)) were analyzed in 32 patients with severe malaria. 10 patients had renal failure, 8 patients had cerebral malaria, and 14 patients had other causes of severity. Prior to treatment, plasma IL-6, and soluble IL-6 receptor were significantly higher in cerebral and/or renal malaria compared with the other group ($p < 0.05$ for both). The highest levels were seen in cerebral malaria ($p < 0.05$ compared with renal malaria or other forms of severe malaria). 24 hr after initiation of therapy, IL-6 levels

dropped but soluble IL-6 receptor levels increased further in all groups. CNTF levels were significantly reduced in cerebral malaria and renal failure compared to moderate severe malaria or healthy controls, and normalized 24 hr after start of treatment. Plasma concentration of gp130 and LIF were not different between malaria patients and healthy controls. We concluded that a) excessive levels of IL-6 could be controlled by a subsequent shedding of the soluble IL-6 receptor, b) in contrast to septicemia, LIF levels are not elevated in severe malaria, and c) low level CNTF expression could contribute to cerebral malaria and/or renal failure. ■

PREDICTING MORTALITY IN PATIENTS WITH MALARIAL ACUTE RENAL FAILURE

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APACHE III scores, calculated within the first 24 hours of admission, were analyzed in 108 patients with acute renal failure due to falciparum malaria who were admitted to the Bangkok Hospital for Tropical Diseases, Thailand. Twelve (11.1%) patients died. The mean APACHE III score was 82.0 ± 25.5 (range, 45-171). There was a close relation between the APACHE III score and the hospital mortality rate. The nonsurvivors had significantly higher APACHE III scores than the survivors, 109.8 ± 36.7 and 75.7 ± 21.6 respectively ($p < 0.001$). Patients with an APACHE III score of ≥ 82 had a 4.2-fold higher risk of dying compared with patients with a lower score (95% CI 1.2-14.7; $p = 0.013$).

Hemodialysis treatment was performed in 97 (89.8%) of the patients. Although the mean APACHE III score for patients who were not treated with hemodialysis (95.9 ± 38.0) was not significantly higher than for patients who received hemodialysis (80.4 ± 23.5 ; $p > 0.05$), the former had a 4.4 times higher risk of dying compared with patients who received hemodialysis (95% CI 1.6-12.3; $p = 0.019$).

Using the APACHE III score and its ability to predict death, we calculated its sensitivity, specificity and accuracy to be 0.92, 0.31 and 0.41 respectively at a cutoff score of 67 points. The area under the receiver operating characteristic (ROC) curve was 0.75.

The APACHE III scoring system correlated well with the mortality of critically ill malaria patients with acute renal failure, although it was not possible to identify individual survivors or nonsurvivors. APACHE III should not be used for individual prognosis or treatment decisions. ■

TREATMENT OF MALARIA ACUTE RENAL FAILURE BY HEMODIALYSIS

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We studied 112 patients with malarial acute renal failure (ARF) during the years 1991 to 1997 at Bangkok Hospital for Tropical Diseases, Mahidol University, Bangkok. Hemodialysis was performed in 101 (90.2%) of these patients. The mean number of times the patients were hemodialysed was 6.5 (range, 1-27). Ninety-three (83.0%) patients were oliguric and the remainder were nonoliguric. Patients who had oliguric renal failure required more hemodialyses and had more complications than the nonoliguric patients. The oliguric patients had an eight-fold higher risk of requiring six or more hemodialyses (95% CI of 1.2-53.9; $p=0.0008$). The overall mortality rate was 10.7% (12 of 112). Eleven of the patients who died were jaundiced and eight of them had cerebral malaria with $GCS \leq 8$. We conclude that hemodialysis is a useful treatment for oliguric and nonoliguric ARF from severe malaria, particularly when initiated early in the course of illness. ■

Published in: Am J Trop Med Hyg 1999;60(2):233-7.

PULMONARY EDEMA AND ARDS IN CEREBRAL MALARIA PATIENTS IN THAILAND

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Pulmonary edema (PE) is a serious complication of falciparum malaria that usually occurs in association with cerebral malaria (CM), acute renal failure (ARF), high parasitemias, or delayed antimalarial treatment. From 1993 to 1996, 120 adult patients admitted to the intensive care unit of the Bangkok Hospital for Tropical Diseases were enrolled in a prospective study to assess the combination of artesunate and mefloquine for the treatment of CM. Twenty-five patients (21%) developed PE and a majority developed complications in other organs as well, especially ARF. All were treated with supplemental oxygen and for adult respiratory distress syndrome (ARDS), positive end-expiratory pressure (PEEP). In most patients (19 of 25), PE was noted on the first day of admission and was associated with higher parasitemias and levels of acidemia, in comparison with patients without PE. Ten of the 25 patients diagnosed with PE developed signs consistent with ARDS. The mean CVP when PE was diagnosed was

markedly lower in ARDS than in non-ARDS patients, supporting the argument that fluid imbalance is not essential for malaria-induced lung injury. All patients with PE were treated with supplemental oxygen and those with ARDS were also treated with positive end-expiratory pressure (PEEP). Seven of 10 patients with ARDS died, 5 within 24 hours of admission, but there were no deaths in the 15 PE patients without ARDS. Early diagnosis and prompt treatment remain important principles to reduce the morbidity and mortality associated with complicated falciparum malaria. This report emphasizes that pulmonary monitoring is important in adults with CM and that ARDS, as in other diseases, is an especially poor prognostic indicator. ■

Published in: Southeast Asian J Trop Med Hyg 1998;29(3):541-5.

THE PHARMACOKINETICS AND PHARMACODYNAMICS OF LUMEFANTRINE (BENFLUMETOL) IN ACUTE UNCOMPLICATED FALCIPARUM MALARIA

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Objective: To conduct a prospective population pharmacokinetic and pharmacodynamic evaluation of lumefantrine during studies of artemether-lumefantrine treatment of uncomplicated multi-drug resistant falciparum malaria.

Methods: Three regimens, A: containing an average adult lumefantrine dose of 1920mg over three days (4 doses), B: 2780mg over three days (6 doses), or C: five days (6 doses) were given to 266 Thai patients. Detailed observations were obtained in 51 hospitalized adults and sparse data were collected from 215 patients of all ages in a community setting.

Results: The population absorption half-life was 4.5 hours. The model based median (5th and 95th percentile) peak concentrations were 6.2 (0.25, 14.8) ug/mL after regimen A, 9.0 (1.1, 19.8) ug/mL after B, and 8 (1.4, 17.4)

ug/mL after C. There was marked variability between patients in the fraction of drug absorbed during acute malaria (coefficient of variation 150%). The fraction increased considerably with clinical recovery, largely as a result of resuming normal food intake; taking a normal meal close to drug administration increased oral bioavailability by 108% (90% CI 64 to 164) $p = 0.0001$. The higher dose regimens gave 60 and 100% higher AUCs and longer median durations for which plasma lumefantrine exceeded the putative *in-vivo* MIC of 280 ug/mL; Regimen B: 252 hrs, C: 298 hrs, compared to A 204 hrs ($p = 0.0001$), and higher cure rates. There was no evidence that lumefantrine prolonged the EKG QTc interval.

Conclusions: Lumefantrine oral bioavailability is very dependent on food, and is poor in acute malaria, but improves markedly with recovery. The high cure rates with the two six dose regimens result from increased AUC values and increased time above the *in-vivo* MIC. ■

The study was supported by the Wellcome Trust, Oxford Tropical Medicine Research Programme, 183 Euston Road London NW1 2BE, UK.

FACTORS INFLUENCING MALARIA ENDEMICITY IN YUNNAN PROVINCE, PR CHINA

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This study was an initial attempt to apply disease mapping through Geographical Information System (GIS) with multiple regression analysis to determine the nature and extent of factors influencing malaria transmission in Yunnan Province, PR China, particularly in border areas. Secondary county-based data covering the period 1990 to 1996 were collected and analyzed. The malaria situation in Yunnan Province as a whole is influenced mainly by the combined effects of the physical environment, the presence of efficient vector species, and the mobile population along international borders with Myanmar, Lao PDR and Vietnam. ■

Published in: Southeast Asian J Trop Med Public Health 1998;29(2):191-200.

RESEARCH ON NEW ANTIMALARIAL DRUGS IN THE BANGKOK HOSPITAL FOR TROPICAL DISEASES

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Clinical trials of new antimalarial drugs (atovaquone, artesunate, artemether, dihydroartemisinin, CGP 56697, pyronaridine, and biguanide-dapsone combinations) for treatment of uncomplicated malaria have been studied in the Bangkok Hospital for Tropical Diseases. Studies of artesunate and artemether have

confirmed the earlier Chinese work. Patients with malaria improved faster following treatment with these artemisinin derivatives compared with other antimalarial drugs. The artemisinin derivatives were all well tolerated and had insignificant side effects.

A clinical trial of oral dihydroartemisinin for the treatment of acute, uncomplicated, falciparum malaria involved 53 adult patients. Each received a total dose of 480 mg over 7 days (120 mg given immediately, followed by 60 mg/day) after being admitted to the Hospital for Tropical Diseases in Bangkok. Most (92%) completed the 28-day follow-up but four patients left the hospital early, for reasons unrelated to their treatment. Most patients showed clinical improvement 1-3 days after starting treatment and none suffered from serious adverse reactions. The cure rate was 90% (44/49). The mean (S.D.) parasite-clearance time was 40.4 (14.1) hr. and the mean fever-clearance time was 37.0 (30.2) hr. Seven patients had a brief increase in parasitemia after initiation of treatment but subsequent counts declined dramatically. Five patients who failed treatment (RI response) were successfully treated with quinine plus tetracycline for 7 days. No RII or RIII responses were observed. These findings indicate that treatment with oral dihydroartemisinin is effective and well tolerated, and that dihydroartemisinin may be suitable as an alternative treatment for acute, uncomplicated, falciparum malaria.

Recently, three new formulations have been developed in Vietnam, Thailand, and the Netherlands which have become available. However, there are some doubts over the source of raw material for production and the formulations made, so we have compared prospectively the efficacy and safety of three different sources and formulations of dihydroartemisinin in 157 patients with uncomplicated falciparum malaria acquired in Thailand in a second trial. Patients were assigned to one of three treatment regimens. Group I received a dose of 200 mg of oral dihydroartemisinin (Cotexin® 20 mg/tablet, Cotec, Beijing, People's Republic of China) on the first day of treatment and then 100 mg of dihydroartemisinin daily for 4 consecutive days for a total dose of 600 mg. Group II received a dose of 200 mg of oral dihydroartemisinin (Vietnamese product, formulated by the Government Pharmaceutical Organization of Thailand) on the first day of treatment and then 100 mg of dihydroartemisinin daily for 4 consecutive days for a total dose of 600 mg. Group III received a dose of 200 mg of oral dihydroartemisinin (Thai product, formulated by the Government Pharmaceutical Organization) on the first day and then 100 mg of dihydroartemisinin daily for 4 consecutive days for a total dose of 600 mg. Results of this study revealed the cure rates in Groups I, II, III were 80%, 85%, 92% respectively. There were no significant differences in either parasite clearance time or fever clearance time among Group I, Group II and Group III ($p > 0.05$). The mean parasite reduction times to 50% and 90% were 11.5 and 18.6 hr for group I, 13.6 and 22.6 hr for Group II, and 10.2 and 17.7 hr for Group III, respectively. Patients in the three treatment groups tolerated the drug well and there were no differences among the groups. No major adverse effects were found.

CGP 56697, a new oral fixed combination of artemether and benflumetol, was tested in a double-blind, randomized, trial in 252 adult patients treated either with CGP 56697 (4 x 4 tablets each containing 20 mg artemether and 120 mg benflumetol, given at 0, 8, 24 and 48 hr), or with mefloquine (3 tablets of 250 mg at initial diagnosis, followed by 2 tablets of 250 mg at 8 hr). Baseline data of the two groups were comparable. The 28-day cure rate with CGP 56697 was lower than with mefloquine (69.3% vs. 82.4%, $p=0.002$). However, CGP 56697 was more effective than mefloquine in parasite clearance time (43 hr vs. 66 hr, $p<0.001$) fever clearance time (32 hr vs. 54 hr, $p<0.005$), and gametocyte clearance time (152 hr vs. 331 hr, $p<0.001$). This study revealed that CGP 56697 is effective against multidrug resistant falciparum malaria in Thailand. Higher doses are being evaluated.

Atovaquone is a novel hydroxynaphthoquinone with broad spectrum anti-protozoal activity. We recently evaluated the antimalarial activity of atovaquone in a series of dose-ranging studies in 317 patients with malaria. Originally, the drug was administered alone. Using atovaquone alone resulted in satisfactory, initial clinical responses in all patients; the mean parasite and fever clearance times were 62 and 53 hr, respectively. However, irrespective of the duration of therapy, overall cure rates were approximately 67%. *In vitro* sensitivity studies on parasites taken from patients prior to treatment and at the time of recrudescence showed a marked decrease in susceptibility to atovaquone in the recrudescence parasites. To improve cure rates, atovaquone was

administered in combination with other drugs with antimalarial activity. Proguanil and tetracycline were chosen due to laboratory evidence of potentiation; doxycycline was selected because it has a longer half-life than tetracycline. Although pyrimethamine did not show laboratory evidence of potentiation with atovaquone, it was chosen as an alternative inhibitor of dihydrofolic acid reductase with a longer half-life than proguanil. Clinical studies with these drug combinations confirmed the laboratory results with marked improvement in cure rates for proguanil, tetracycline, and doxycycline; pyrimethamine showed only minimal improvement. Proguanil was subsequently selected as the preferred drug partner because of its long record of safety and the ability to use the drug in pregnant women and children. Of the 104 patients with falciparum malaria treated with atovaquone plus proguanil for 3-7 days, 101 were cured and had virtually no adverse side effects. The combination of atovaquone and proguanil also was effective in eliminating erythrocytic forms of *P. vivax*, but parasitemia recurred in most patients.

One hundred and one adult patients with acute uncomplicated falciparum malaria were treated with pyronaridine. Sixty-nine patients (Group I) received pyronaridine 1,200 mg over a three-day period and 32 patients (Group II) received 1,800 mg of pyronaridine over a five-day period. Cure rates for the two groups were 63% (38 of 60) for Group I and 88% (23 of 26) for Group II ($P < 0.05$). No RII or RIII type response was seen. Mean fever and parasite clearance times were not significantly different in the two groups. The drug was well-tolerated. *In vitro* drug sensitivity tests of the paired parasite isolates obtained prior to treatment and after recrudescence indicated that the *Plasmodium falciparum* isolates of the successfully treated patients had a lower mean concentration for 50% inhibition of growth (IC_{50}) and a much narrower range of the individual IC_{50} values (15.69 ± 3.82 ng/ml [mean (SD)] as compared with those from the recrudescence cases (22.98 ± 12.05 ng/ml). Nevertheless, there was no evidence of an increase in the IC_{50} and IC_{95} values after recrudescence. The results of the study show that pyronaridine alone at a total dose of 1,800 mg given over five days is well-tolerated in patients suffering from acute uncomplicated malaria and has evident activity against multidrug-resistant falciparum malaria. However, it cannot be recommended for use in Thailand as long as the recrudescence rate is as high as 12%. Further studies of its combinations with other antimalarial drugs are needed. Recently we have studied the pharmacokinetics and efficacy of the new formulation of pyronaridine and results are encouraging.

Combinations of dapson with proguanil or chlorproguanil have proved effective in the treatment of chloroquine-resistant falciparum malaria in Africa and for prophylaxis in Asia. These combinations have not been used for treatment in areas with multi-drug-resistant parasites such as in Thailand. Combinations of dapson (approximately 4 mg/kg) plus either proguanil (approximately 8 mg/kg; DP regimen; $N = 10$) or chlorproguanil (approximately 1.4 mg/kg; DC regimen; $N = 16$) were given once a day for 3 days to adult Thai patients with acute, uncomplicated, falciparum malaria. The two regimens were well tolerated and had no side-effects, but the cure rates, assessed at 28-day follow-up, were only 10% for DP (60% with RI response and 30% with RII) and 14% for DC (29% with RI response and 57% with RII). The mean (S.D.) fever-clearance times in those patients who were cured (S) or whose infections recrudesced (RI response) were 103 (56) h for those given DP and 90 (42) h for those given DC. The corresponding parasite-clearance times were 83 (46) for DP and 53 (21) h for DC. *In-vitro* susceptibility testing of isolates obtained both before treatment and at recrudescence demonstrated marked resistance to cycloguanil, dapson, chloroquine and mefloquine. The results demonstrate that short-course treatment with dapson plus either proguanil or chlorproguanil is ineffective for the treatment of falciparum malaria in Thailand. ■

Published in: Tokai J Exp Clin Med 1998;23(2):69.

DIFFERENT PLASMA LEVELS OF CIRCULATING CELL ADHESION MOLECULES IN FALCIPARUM MALARIA PATIENTS ACCORDING TO DISEASE SEVERITY

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One of the most prominent pathological features of falciparum malaria is the sequestration of infected red blood cells (IRBCs) in small blood vessels, which is considered to be a major cause of cerebral malaria. It is clear that several different host molecules, including intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), act as receptors for IRBCs *in vivo*. Expression of ICAM-1 on the human vascular endothelium can be upregulated by the proinflammatory cytokines, tumour necrosis factor (TNF) and interleukin 1 α (IL1 α). These cytokines are present at high levels in the plasma of malaria-infected children and elevated levels are related to disease severity. Thus high levels of these cytokines may exacerbate IRBC sequestration by upregulating ICAM-1 expression on the endothelium. A direct measurement of expression of adhesion molecules (CAMs) on the cell surface is difficult. It has been shown, however, that CAMs expression on the endothelial cells correlates with plasma levels of circulating adhesion

molecules (cCAMs) which is shed into the circulation from those cells. Cell adhesion molecules are well known to play an important role during immune responses. Circulating forms of these molecules have been described pathophysiologically correlated with a variety of inflammatory and infectious diseases (e.g. AIDS), graft rejection and autoimmune diseases.

In this study, we examined plasma levels of circulating forms of ICAM-1, ICAM-2, ICAM-3, VCAM-1, and ELAM-1 (cICAM-1, cICAM-2, cICAM-3, cVCAM-1, and cELAM-1 respectively) in patients with complicated or uncomplicated malaria and compared them to uninfected healthy persons. As part of a large scale study on cerebral malaria, plasma samples were obtained from malaria patients who were admitted to the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, on admission day, and Thai volunteers who were not suffering from malaria. Plasma samples were also obtained from Japanese volunteers who had had no experience of malaria. Malaria patients were divided into two groups, mild, that is an uncomplicated, malaria group and a complicated malaria group. The latter was further divided into moderate, severe, and highly severe malaria groups according to the severity of clinical manifestations including central nervous dysfunction, anemia, hypoglycemia and so on. All samples were stored frozen at -20°C until used. Randomly, 20 samples from each malaria group (mild, moderate, severe, or highly severe group) and Thai uninfected volunteers and 13 samples from healthy Japanese uninfected volunteers were chosen and examined. Plasma levels of all cCAMs were measured by a quantitative enzyme-linked immunosorbent assay.

Plasma levels of all cCAMs examined were significantly higher in malaria patients compared with uninfected Thai and Japanese persons. The results also show that among malaria patients, cICAM-1 and cELAM-1 levels were significantly, and cVCAM-1 was slightly, higher in the complicated malaria groups compared with the uncomplicated malaria groups. No differences between patients with complicated and uncomplicated malaria were observed concerning cICAM-2 and cICAM-3. These results provide evidence that plasma levels of cICAM-1 and cELAM-1 correlate with malaria severity and thus those are involved in the pathophysiology of complicated malaria. In this study we could not differentiate between the plasma levels of cCAMs from patients with cerebral malaria and those with severe malaria without cerebral involvement because of limited numbers of samples. The functional roles of those cCAMs in disease have remained unsolved. As cCAMs can interfere with intercellular adhesion, the high level of cCAMs in malaria patients could contribute to the impairment of immune responses resulting in progression of the disease. On the other hand, at a concentration lower than we have detected in the plasma of malaria patients, cICAM-1 has been shown to be enough to inhibit IRBC binding to ICAM-1 in an *in vitro* binding assay. Understanding the pathophysiological function of such cCAMs may give rise to new approaches to the treatment and diagnosis of complications of malaria. ■

Published in: *Tokai J Exp Clin Med* 1998;23(2):79-80.

LACK OF SIGNIFICANT ASSOCIATION BETWEEN ROSETTE FORMATION AND PARASITIZED ERYTHROCYTE ADHERENCE TO PURIFIED CD36

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The ability of *Plasmodium falciparum* infected erythrocytes from 162 Thai patients with uncomplicated malaria, 82 patients with severe malaria and 19 patients with cerebral malaria to form rosettes *in vitro* was studied. Of 263 isolates, 62 were evaluated for their adherence to different target molecules. We found that wide variation occurred in isolates from all groups in the level of rosette formation and adherence to CD36, intracellular adhesion molecule-1, thrombospondin and chondroitin sulfate A. No statistically significant correlation between the magnitude of rosette formation

and disease severity was found ($p > 0.05$). In addition, our results from the use of purified CD36 as an adherence receptor showed no association between the degree of rosetting and the level of cytoadherence ($p > 0.05$, $r = -0.04$). Our data provide evidence that rosette formation and cytoadherence involve different molecular mechanisms and both phenomena can occur in all manifestations of the disease. ■

Published in: Southeast Asian J Trop Med Public Health 1998;29(1):41-5.

EFFICACY AND SAFETY OF ATOVAQUONE/PROGUANIL COMPARED WITH MEFLOROQUINE FOR TREATMENT OF ACUTE PLASMODIUM FALCIPARUM MALARIA IN THAILAND

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The increasing frequency of therapeutic failures in falciparum malaria underscores the need for novel, rapidly effective antimalarial drugs or drug combinations. Atovaquone and proguanil are blood schizonticides that demonstrate synergistic activity against multi-drug-resistant *Plasmodium falciparum in vitro*. In an open-label, randomized, controlled clinical trial conducted in Thailand, adult patients with acute *P. falciparum* malaria were randomly assigned to treatment with atovaquone and proguanil hydrochloride (1,000 mg and 400 mg, respectively, administered orally at 24-hr intervals for three doses) or mefloquine (750 mg administered orally, followed 6 hr later by an additional 500-mg dose). Efficacy was

assessed by cure rate (the percentage of patients in whom parasitemia was eliminated and did not recur during 28 days of follow-up), parasite clearance time (PCT), and fever clearance time (FCT). Safety was assessed by sequential clinical and laboratory assessments for 28 days. Atovaquone/proguanil was significantly more effective than mefloquine (cure rate 100% [79 of 79] vs. 86% [68 of 79]; $P < 0.002$). The atovaquone/proguanil and mefloquine treatments did not differ with respect to PCT (mean = 65 hr versus 74 hr) or FCT (mean = 59 hr versus 51 hr). Adverse events were generally typical of malaria symptoms and each occurred in $< 10\%$ of the patients in either group, with the exception of increased vomiting found in the atovaquone/proguanil group. Transient elevations of liver enzyme levels occurred more frequently in patients treated with atovaquone/proguanil than with mefloquine, but the differences were not significant and values returned to normal by day 28 in most patients. The combination of atovaquone and proguanil was well tolerated and more effective than mefloquine in the treatment of acute uncomplicated multidrug-resistant falciparum malaria in Thailand. ■

Published in: Am J Trop Med Hyg 1999;60(4):526-32.

SERUM PROCALCITONIN LEVELS IN SEVERE *PLASMODIUM FALCIPARUM* MALARIA

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Levels of procalcitonin (ProCT) have been found to be elevated in individuals with severe bacterial infections such as sepsis and peritonitis, and this correlates well with the severity of the disease. Recently, increased levels have been described in melioidosis and *Plasmodium falciparum* malaria. In this study, ProCT levels were measured in 27 Thai patients with complicated malaria before and during/after treatment with artesunate and mefloquine. Initial parasite counts averaged 290,680/μl (range = 533-1,147,040). On admission, ProCT levels were elevated in all but one patient (median = 40 ng/ml, range = 0.04-662, normal values < 0.5 ng/ml). With treatment, levels decreased to 1.3 ng/ml (range = 0.01-6.5). Nitrite/nitrate levels in patients were higher than in controls

throughout the study. The ProCT levels correlated with initial parasite density ($P < 0.05$), which is a marker of disease severity, and with nitrite/nitrate levels ($P < 0.05$). Based on the changes of ProCT levels over the course of the disease a possible role in the acute-phase reaction seems likely. ■

Published in : *Am J Trop Med Hyg* 1998;59(6):860-3.

A DOUBLE BLIND TRIAL OF INSECT REPELLENTS IN THE PREVENTION OF MALARIA IN PREGNANCY

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The western border of Thailand harbors the most multi-drug resistant *Plasmodium falciparum* malaria in the world. This is particularly problematic for malaria during pregnancy, since there are no safe and effective chemoprophylactic drugs. Insecticide impregnated bednets did not reduce the incidence of falciparum parasitemia and because malaria is an important cause of maternal death, low birth weight and anemia. We conducted a double-blind randomized controlled intervention trial to assess the efficacy of a mosquito repellent, DEET (N, N-diethyl-m-toluamide), in preventing malaria in pregnancy in an area of low and seasonal transmission. Eight hundred and ninety seven pregnant women, with a gestational age of 12-28 weeks, were randomly assigned to receive, either thanaka alone (*Limonia acidissima*), a popular cosmetic, or 20% DEET and

thanaka, daily, for the duration of pregnancy. Weekly malaria smears and fortnightly hematocrits were carried out to measure the incidence of malaria and anemia, respectively. Despite excellent compliance, the incidence of *P. falciparum* was too low to measure a significant protective efficacy, although there was a trend in favour of a reduction of *P. falciparum* and *P. vivax* infections by 28% and 9%, respectively, in the DEET group. Further field-based studies, including women in the first trimester of pregnancy, should be considered in areas where there are no effective preventive measures for multidrug resistant *P. falciparum*, and where transmission is significant. ■

The study was supported by the Wellcome Trust, Oxford Tropical Medicine Research Programme, 183 Euston Road London NW1 2BE, UK.

FACTORS AFFECTING ATTENDANCE AT ANTENATAL CLINICS AND USE OF MOSQUITO REPELLENTS AS ANTIMALARIAL CONTROL MEASURES IN PREGNANCY

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run by Karen staff was also another reason for compliance. No association could be found between compliance to repellent and the formulation used, literacy rates, risk of malaria in pregnancy, or to the use of bednets. The use of thanaka, a local cosmetic, as the base for DEET repellent, proved extremely popular. The excellent compliance with these antenatal malaria control measures was attributed largely to the extensive involvement of local health workers and the use of local products. ■

The study was supported by the Wellcome Trust, Oxford Tropical Medicine Research Programme, 183 Euston Road London NW1 2BE, UK.

RANDOMIZED DOSE-RANGING STUDY OF THE SAFETY AND EFFICACY OF WR 238605 (TAFENOQUINE) IN THE PREVENTION OF RELAPSE OF *PLASMODIUM VIVAX* MALARIA IN THAILAND

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WR 238605 is an 8-aminoquinoline developed for the radical cure of *Plasmodium vivax*. Forty-four *P. vivax*-infected patients were randomly assigned to 1 of 4 treatment regimens: 3 groups received a blood schizonticidal dose of chloroquine followed by WR 238605: group A (n = 15) received 300 mg daily for 7 days; group B (n = 11), 500 mg daily for 3 days, repeated 1 week after the initial dose; group C (n = 9), 1 dose of 500 mg. A fourth group D (n=9) received chloroquine only. Among patients who completed 2-6 months of follow-up (n=23), there was 1 relapse in group B (day 120) and 1 in group C (day 112). Among patients treated with chloroquine only, there were 4 relapses (day 40, 43, 49, and 84). WR 238605 was safe, well tolerated, and effective in preventing *P. vivax* relapse. ■

Published in : J Infect Dis 1999;180:1282-7.

COMPLICATED MALARIA IS ASSOCIATED WITH DIFFERENTIAL ELEVATIONS IN SERUM LEVELS OF INTERLEUKINS 10, 12, AND 15

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Complicated malaria, caused by *Plasmodium falciparum*, is characterized by multiple organ dysfunction. The pathogenesis of complicated malaria involves complex host-parasite interactions that include polarized cytokine responses. Recently, correlates between Th1-like and Th2-like cytokines, especially interleukin-10 (IL), IL-12, and TNF- α , and specific types of organ dysfunction have been noted. Here, we measured IL-10, IL-12, and for the first time, IL-15, in 19 patients aged 16-55 years old with complicated malaria on days 0 (admission), 3, 7, and 14. For analysis, patients were grouped together or subcategorized into hyperparasitemias or cerebral malaria (CM). For IL-10, a dramatic increase was noted on admission, followed by a reduction toward

control values that closely paralleled parasite clearance. For IL-12, modest but persistent increases were noted over the entire 14-day period that did not correlate with parasitemia. In general, especially on days 0 and 3, hyperparasitemic patients had, in comparison with CM patients, higher IL-10 and IL-12 levels. In contrast, IL-15 was generally below detection in most samples. These results provide further insight into the pathogenesis of complicated malaria by strengthening the contention that cytokines such as IL-10 and IL-12 are involved in modulating the immune response to *P. falciparum*. ■

Published in: *Southeast Asian J Trop Med Public Health* 1999 (in press).

LOW CD8⁺T LYMPHOCYTE RESPONSE TO *P. FALCIPARUM* CIRCUMSPOROZOITE PROTEIN IN NATURALLY-EXPOSED MALARIA ENDEMIC POPULATIONS IN THAILAND

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Cytotoxic T lymphocytes (CTLs) specific for epitope (s) within the circumsporozoite (CS) protein of malaria sporozoite have been shown to play an important role in protective immunity against malaria. Human CTLs against the potential epitope at carboxyl terminal region of CS protein of *P. falciparum* 7G8 strain (Pf7G8CS 368-390) were determined in 36 falciparum malaria patients and 10 healthy controls. Four of 36 individuals and none of the healthy controls developed

Pf7G8CS 368-390 specific CTL activity. The CTL activity was antigen specific and CD8⁺ T cell dependent. Although low CTL response has been determined, the study seems to indicate that there was a correlation between initial parasitemia and the specific Pf7G8CS 368-390 CTL activity. The correlation between such CTL activity and anti-R32tet32 antibody levels among individuals with previous malaria experiences was found, which was in contrast to those among individuals with recent malaria infection. All these 4 positive CTL individuals had at least two episodes of clinical malaria while all 25 individuals who were first exposed to malaria could not be found to have such specific CTL response. These results showed that individuals with a history of natural endemic exposure to *P. falciparum* sporozoite developed low specific CTL response to Pf7G8CS 368-390, and recent sporozoite exposures might be a prerequisite for generation of such CS protein specific CTL response. ■

Submitted to: *Southeast J Trop Med Public Health* (1999).

LOW LEVELS OF TGF- β 1 IN PLASMA OF THAILAND TANZANIAN PATIENTS WITH CEREBRAL MALARIA

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Transforming growth factor- β (TGF- β) is a prototype of a multifunctional cytokine. It plays an important role in immune modulation acting both as a pro- and anti-inflammatory cytokine depending on cell types, environment and concentration. The dual nature of this cytokine makes it a potential target as an immunomodulatory pharmacological substance with potential use in reducing malaria pathology in patients. As imbalance of the cytokine network is thought to be behind pathological manifestation of many diseases, thus a better understanding of the biological part played by TGF-

β in disease outcome could lead to its use as a pharmacologically active substance to maintain a fair balance between the effects brought by other cytokines that have both protective and pathogenic effects during malaria infection. We have sought to evaluate the position of this cytokine in malaria severity in relation to other cytokines suspected to be instrumental in malaria disease severity.

The study was conducted in children who presented at a district hospital, Muheza, Tanga Region, north-western Tanzania and at two health centers in Dar-es-Salaam Region, eastern Tanzania. The mean age of the Tanzanian children with cerebral malaria was 1.34 years. Aparasitemic and asymptomatic children were recruited from the same areas in which the hospitalized children lived. Thai plasma samples were taken from adults with cerebral, severe and uncomplicated malaria, admitted at the Bangkok Hospital for Tropical Diseases, and who had contracted the disease from neighboring provinces where malaria is endemic. Plasma was immediately separated once venous blood was collected. Each sample was frozen at -70°C to avoid denaturation of cytokines in the plasma.

Plasma levels of TGF- β 1, IL-10 and TNF- α were determined by solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) with commercially available kits (Genzyme, Cambridge, MA). The procedure followed was as per manufacturer's instructions. Briefly, TGF- β I standard stock solution was activated by mixing together 440 μl of sample diluent, 20 μl of TGF- β 1 standard, 20 μl of 1N HCl. The mixture was mixed and incubated for one hour, then finally, 20 μl of 1N NaOH were added to stop the reaction. The final concentration of this activated standard stock solution is 4 ng/ml. The standard was then diluted serially to the desired concentrations, from which a standard curve was constructed. Essentially the same procedure was followed for the activation of TGF- β 1 in serum samples except that 450 μl of sample diluent were used for serum samples and 15 μl of NaOH was used. Then, 100 μl of samples or standards were added to duplicate wells and incubated at 37°C for 1 hour. Plates were washed and bound cytokines were detected by anti-TGF- β 1 HRP-conjugate and substrate reagent, respectively. For IL-10 and TNF- α , the samples were diluted 1:4 and the rest of the procedure was as per the kit's instructions (Genzyme). Mann-Whitney U test was used to compare means between different groups and Kruskal-Wallis (ANOVA) was used to compare means in differing malaria severity. Two-tailed P-values of lower than 0.05 were considered significant.

Thai adult cerebral malaria patients had significantly lower concentrations of TGF- β 1 compared to normal controls ($P < 0.001$) and uncomplicated subjects ($P < 0.001$), respectively. The same significant plasma level was observed with severe malaria against control ($P < 0.02$); while plasma concentrations of TGF- β 1 between severe and uncomplicated were not significantly different. Severe malaria patients differed significantly from cerebral patients ($P < 0.001$). We also observed elevated plasma levels of IL-10 ($P < 0.01$) in Thai adult patients with cerebral malaria compared with normal controls. Comparison of the levels of TGF- β 1 in Thai adults and Tanzanian children showed a significant difference ($P < 0.001$).

The lowest levels of IL-10 were found in aparasitemic and asymptomatic controls. IL-10 levels of cerebral malaria patients were significantly higher than controls in both the Thai and Tanzanian study groups ($P < 0.01$).

A significant difference in the mean TNF- α levels between cerebral malaria patients and controls was found ($p < 0.05$). In the Tanzanian study group, the mean values were 61.15 ± 71.64 pg/ml and 10.67 ± 26.13 pg/ml for cerebral and control subjects, respectively. In contrast, for adults with cerebral malaria, TNF- α levels were not elevated significantly when compared with control groups. ■

EFFICACY OF THE THREE DAY SIX-DOSE REGIMEN OF ARTEMETHER-LUMEFANTRINE, IN THE TREATMENT OF MULTIDRUG RESISTANT FALCIPARUM MALARIA

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The efficacy and safety of the six-dose regimen of artemether-lumefantrine were assessed in an open randomized trial in children and adults presenting with acute, uncomplicated *P. falciparum* malaria in Thailand. A total of 200 patients were enrolled in two centres: 150 received artemether-lumefantrine (i.e. median [interquartile range] of 9.6 mg/kg [8.7, 10.7] of artemether, and 57.9 mg/kg [52.4, 64] of lumefantrine), and 50 patients a combination of artesunate [12 mg/kg over 3 days] and mefloquine [25 mg/kg]. All patients had rapid initial clinical and parasitological responses. The cure rates were high: 97.7% (95% CI 93.5, 99.5%) for artemether-lumefantrine and 100% (95% CI 92.5, 100%) for artesunate-mefloquine. The six-dose regimen of artemether-lumefantrine was better tolerated and was as effective as artesunate-mefloquine; the current standard treatment in this area of multi-drug resistant *P. falciparum* malaria. ■

The study was supported by the Wellcome Trust, Oxford Tropical Medicine Research Programme, 183 Euston Road London NW1 2BE, UK.

CR1 DENSITY POLYMORPHISM ON ERYTHROCYTES OF FALCIPARUM MALARIA PATIENTS IN THAILAND

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Circulating immune complexes previously have been shown to occur in both experimental animals and humans with malaria and to induce pathological consequences through their deposition in various organs.

CR1 on erythrocytes plays an important role in the clearance of immune complexes from the circulation by transporting them to macrophages in the liver and spleen. The number of CR1 molecules expressed on erythrocytes is genetically determined in healthy individuals by an autosomal co-dominant bi-allelic system. Erythrocytes from different normal individuals may show up to 10-fold

variation in their number of CR1 per cell. The genotype associated with low expression of CR1 molecules on the surface of erythrocytes is related to an additional *HindIII* restriction enzyme cleavage site located in an intron within the structural gene on chromosome 1. The CR1 genotype is determined by PCR amplification using the genomic DNA as a template followed by *HindIII* restriction enzyme digestion and agarose gel electrophoresis.

Although this method has been successfully applied to populations of various races, Herrera *et al* reported the absence of an association between this genomic polymorphism and CR1 expression among African-Americans. Therefore, we performed a microliter plate ELISA, which confirmed the usefulness of this genomic polymorphism for predicting the CR1 expression in our study population.

To assess the relationship between this CR1 density polymorphism and disease severity, a total of 117 Thai patients with falciparum malaria were analyzed. ■

CLINICAL MALARIA AND TREATMENT OF MULTIDRUG RESISTANT FALCIPARUM MALARIA IN THAILAND

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Clinical manifestations of malaria are nonspecific and range from asymptomatic to severe. The clinical presentations reflect complex interactions between the host, the environment, and the parasites. Signs and symptoms include fever, headache, muscle pain, abdominal pain, anorexia, nausea, vomiting, hepatosplenomegaly, jaundice and dark urine. In mild malaria, these signs and symptoms cannot differentiate malaria from the common cold, influenza or other systemic diseases. Fever and malaise in malaria are believed to result from the release of endogenous cytokines [eg. interleukin 1, 6 & 8 (IL-1, IL-6, IL-8) and tumour necrotic factor- α (TNF- α)] in response to parasite antigens. Other signs and symptoms of malaria are also associated with the rupture of parasitized red cells. In severe malaria, the clinical manifestations included cerebral malaria, pulmonary edema, renal failure, anemia, and jaundice. Signs and symptoms of cerebral malaria are as follow, alteration of consciousness, coma, dysconjugated eye-balls and convulsions. Among fatal cases, 80% died within the first 48 hours of admission while in the rest, death resulted from complications such as acute renal failure, pulmonary edema, bacterial infection, and lactic acidosis. 92% of the survivors had complete recovery.

Treatment of multidrug resistant falciparum malaria in Thailand is complicated. New antimalarial drugs have been investigated at the Bangkok Hospital for Tropical Diseases in recent years. Artemisinin derivatives such as artesunate, artemether, arteether, dihydroartemisinin are also tested at the Bangkok Hospital for Tropical Diseases. Artesunate and artemether alone, with a total dose of 600 to 750 mg produced cure rates of 80 to 95%. Artesunate suppositories have been proved successful for the treatment of severe malaria. The artemisinin derivatives, when used in combination with mefloquine, gave improved cure rates to 95-100%. Dihydroartemisinin alone, with a total dose of 480 mg given over 5 days, gave a cure rate of 90%. At present, studies with the combination of artemisinin derivatives plus mefloquine in various doses and durations of treatment are being investigated. Until proven otherwise, the drug combinations are still recommended for all adult patients suffering from acute uncomplicated falciparum malaria contracted in multidrug resistant areas.

In severe malaria, the choice of antimalarial chemotherapy depends on the clinical severity, the drug sensitivity of the parasites, and the availability and preparation of the drug. Quinine is a widely available drug. Qinghaosu and its derivatives have been used successfully in treating both uncomplicated and severe falciparum malaria. Their effectiveness in eliminating the parasites has been extensively documented, however, the recrudescence rate is rather high (10-30%). In treating severe malaria, early diagnosis and early treatment are vital and the aim is to save the patient's life. Prompt administration of an adequate and effective antimalarial drug is needed once the diagnosis is made. Other symptomatic and supportive treatment include careful monitoring of fluid intake and urine output, frequent observations for complications with appropriate treatment and good nursing care. ■

Published in : Jpn J Trop Med Hyg 1999;27(1):181-8.

GUIDELINE IN MANAGEMENT OF SEVERE MALARIA

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Severe malaria remains a major cause of mortality in the world. Malaria can mimic many diseases and there is no absolute diagnostic clinical feature. High index of suspicious symptoms is a clue for clinical diagnosis. Previous travel history to an endemic area should be elicited in all, and in particular, febrile patients. Management of severe malaria needs potent antimalarial drugs and intensive care. Artemisinin derivatives can be used alternatively to quinine. Dexamethasone and mannitol have no proven beneficial effects in the management of cerebral malaria. In pulmonary edema, patients for whom hydration assessment is difficult to monitor, central venous pressure evaluation may be useful. Acute renal failure patients may need dialysis until the uremic syndrome subsides or patients can void urine. Most severe malaria patients have thrombocytopenia; however platelet concentrate is indicated only in those patients with systemic bleeding. Morbidity and mortality will be reduced in severe malaria patients with early diagnosis and prompt treatment. ■

Published in: JAMA 1999 (in press).

POPULATION PHARMACOKINETICS OF MEFLOROQUINE IN PATIENTS WITH ACUTE FALCIPARUM MALARIA

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Objective: To construct a population pharmacokinetic model for mefloquine in the treatment of falciparum malaria.

Background: Mefloquine is the treatment of choice for multi-drug resistant falciparum malaria. The factors which influence the pharmacokinetic properties of mefloquine in acute malaria are not well characterized.

Methods: The pharmacokinetic properties of mefloquine were evaluated in 257 patients with acute falciparum malaria using non-linear mixed effect modelling. Two different oral dose regimens were used; a split dose of 15 mg base /kg initially followed by 10 mg/kg 24 hours later (n=159), and a single dose of 25 mg/kg (n=98). Mefloquine was combined with artesunate in 105 (41%) subjects (74 receiving a split dose and 31 receiving a single dose).

Results: Inter-subject variability in oral clearance (CL/F) and the apparent volume of distribution (V/F) ranged from 15% up to 56%. Assuming oral clearance was unaffected by dose regimen, splitting the mefloquine dose

increased the relative oral bioavailability by 50% (95% CI: 36%, 65%) for monotherapy and by 20% (95% CI: 3%, 40%) for combined therapy. The total apparent volume of distribution (V/F) was therefore significantly lower in patients receiving split doses of mefloquine monotherapy (mean[95% CI]: 8.14[7.49,8.86] l/kg) compared to a single dose (20.37[16.26,25.51]l/kg). Patients who received mefloquine monotherapy and cleared parasitemia in less than 48 hours had a significantly higher AUC₀₋(independent of any confounders, compared to patients with slower parasite clearance (geometric mean [95% CI]: 50373[46121-55017] vs 45583[42306-49125] ng/ml(day).

Conclusions: The pharmacokinetic properties of mefloquine in malaria were relatively unaffected by demographic variables or disease severity. Splitting the 25 mg/kg mefloquine dosage improves oral bioavailability and the therapeutic response in the treatment of acute falciparum malaria. ■

The study was supported by the Wellcome Trust, Oxford Tropical Medicine Research Programme, 183 Euston Road London NW1 2BE, UK.

MANAGEMENT OF MALARIA WITH ACUTE RENAL FAILURE

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In parts of the world, such as Africa, where *Plasmodium falciparum* is endemic and its transmission stable, severe malaria affects mainly children. Cerebral malaria and severe anaemia are common, but multi-organ failure involving the kidneys or liver is very rare. Surviving children develop immunity and thus in adults rarely develop severe disease. In contrast, in other tropical countries where transmission of *P. falciparum* is unstable and the risk of infection is low, severe malaria can occur at any age. Severe malaria is defined

as parasitaemia greater than 5% or vital organ dysfunction. Acute renal failure (ARF) is a common complication of severe falciparum malaria in non-immune individuals.

At the Bangkok Hospital for Tropical Diseases, 5,210 patients with falciparum malaria were admitted during the period 1991-1997, of whom 112 patients (2.12%) had ARF. In a recent study of 560 cases of severe adult malaria in Vietnam, 28% of patients had renal failure on admission and 41% at some stage, with 14% overall requiring dialysis. Overall, however, ARF is not a common complication of malaria. During the Vietnam War, the reported incidence was 19 cases in 3,300 malaria admissions in 1965/6 and 8 of 2003 admissions in 1966/7. ■

CHARACTERISTICS OF FALCIPARUM ISOLATES IN THAILAND USING AN *IN VITRO* HUMAN LUNG ENDOTHELIAL CELLS MODEL

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The purpose of this study was to identify different characteristics of falciparum malaria isolates in order to determine their interactions. 69 Thai isolates (27 complicated and 42 uncomplicated cases) were used. Our results show an association between cytoadherence phenotype and malaria severity ($p=0.05$). PRBCs from complicated patients significantly bound to HLECs via ICAM-1 and CSA compared to those from uncomplicated cases ($p<10^{-4}$). On the other hand, PRBCs from uncomplicated cases adhere more via CD36 ($p<10^{-3}$). No significant difference was observed between the binding of PRBCs via E-selectin and VCAM-1 in both groups ($p=0.6$). This study also reports the absence of association between

cytoadherence profile and rosette formation ($p=0.1$), a positive correlation between the IC_{50} 's of some antimalarial drugs and the number of PRBCs having adhered to HLECs or having rosetted. We observed a strong negative correlation between the platelets and PRBCs having adhered to HLECs ($p=0.007$). These results help to shed light on the role of platelets in the pathophysiology of severe malaria and provide useful information about the interactions between these different factors. ■

Submitted to: J Infect Dis 1999.

NO EVIDENCE OF CARDIOTOXICITY DURING ANTIMALARIAL TREATMENT WITH ARTEMETHER-LUMEFANTRINE

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Artemether and lumefantrine (benflumetol) is a new combination effective against multidrug-resistant falciparum malaria. Lumefantrine is a racemic fluorene derivative with the chemical name 2-dibutylamino-1-[2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluoren-4-yl]-ethanol. It conforms, structurally, to the aryl-amino alcohol group of antimalarials including quinine, mefloquine and halofantrine. Other antimalarials, notably quinine, and to a greater extent quinidine and halofantrine, are known to prolong the QTc-interval at therapeutic dosages, and halofantrine has been associated with sudden death. Artemether, is a methyl-ether, derivative of dihydroartemisinin derived from artemisinin (Qinghaosu). Artemether and the closely related compound arteether, given in high doses by intramuscular injection prolong the

QTc-interval in rats and dogs, which has given rise to concern that similar effects could occur in clinical use, but there is no evidence from large prospective clinical studies of any cardiotoxicity with this compound in man. Artemether-lumefantrine has usually been given as a four dose regimen comprising 320 mg artemether and 1920 mg lumefantrine for adults. In Thailand, two studies have been conducted with a 6-dose regimen which has proved highly effective and well tolerated. These large-dose optimizing studies with higher dose regimens provided the opportunity to conduct detailed electrocardiographic studies and to relate any changes observed to the plasma concentrations of lumefantrine. ■

The study was supported by the Wellcome Trust, Oxford Tropical Medicine Research Programme, 183 Euston Road London NW1 2BE, UK.

FREQUENCY OF PRURITUS IN *PLASMODIUM VIVAX* MALARIA PATIENTS TREATED WITH CHLOROQUINE IN THAILAND

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Chloroquine-induced itch in black skinned African malaria patients is common and frequently leads to poor compliance or treatment defaulting. To assess the frequency and severity of chloroquine-induced pruritus in an Asian population, we reviewed case records of 1189 *Plasmodium vivax* malaria patients admitted to the Bangkok Hospital for Tropical Diseases from 1992-1997 treated with chloroquine (25 mg/kg over 3 days). The majority of patients were Thais and ethnic Burmese (light brown skin), referred from the western border of Thailand. Overall, there were only 23 patients (1.93%) with complaints of chloroquine induced pruritus. Of these, 12 cases (52%) had palm and sole involvement, 8 cases (35%) had generalized pruritus including the palms and soles, and 3 (13%) had palm itching only. One patient developed pruritus on the palms and soles on 2 consecutive admissions. The pruritus was mild in that it did not

interfere with daily activity, was reduced in intensity by antihistamine therapy, and did not affect the patient's willingness to complete the chloroquine regimen. Therapeutic responses in the 23 patients with chloroquine itch was similar to those without itch. Among the itch patients, there was no association with gender or level of parasitemia. Our findings confirm that the frequency of chloroquine-induced pruritus in Asian patients treated with chloroquine for *Plasmodium vivax* malaria is low. In comparison with black-skinned Africans, this may be related to pharmaco-genetic factors, the malaria species being treated, drug metabolism, drug-parasite interactions, or a lesser affinity of chloroquine for less pigmented skin. ■

Published in: *Trop Doc* 1999 (in press).

ATOVAQUONE AND PROGUANIL HYDROCHLORIDE FOLLOWED BY PRIMAQUINE FOR TREATMENT OF *PLASMODIUM VIVAX* MALARIA IN THAILAND

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Chloroquine-resistant *Plasmodium vivax* malaria has been reported in several geographic areas. The *P. vivax* life cycle includes dormant hepatic parasites (hypnozoites) that cause relapsing malaria weeks to years after initial infection. Curative therapy must therefore target both the erythrocytic and hepatic stages of infection. We conducted an open-label study to evaluate the efficacy and tolerability of a sequential regimen of a combination of atovaquone (1000 mg) and proguanil hydrochloride (400 mg), once daily for 3 days, followed by primaquine (30 mg daily for 14 days) for treatment of vivax malaria. All 46 patients who completed the 3-day course of atovaquone/

proguanil cleared their parasitemia within 2 to 6 days. During a 12-week follow-up period in 35 patients, recurrent parasitemia occurred in two. Both recurrent episodes occurred 8 weeks after the start of therapy, consistent with relapse from persistent hypnozoites rather than recrudescence of persistent blood-stage parasites. The dosing regimen was well tolerated. Results of this trial indicate that atovaquone/proguanil followed by primaquine is effective for treatment of vivax malaria. ■

Published in: *Am J Trop Med Hyg* 1999 (in press).

APPLICATION OF YEAST ENOLASE AS ANTIGEN FOR IMMUNODIAGNOSIS OF MALARIA

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values against yeast enolase for the following 4 weeks after admission were also examined for sera from falciparum malaria patients. Patients with severe malaria showed increasing RFU values as the clinical course progressed. However, in the mild cases, each RFU value stayed unchanged during the course. We concluded that yeast and rabbit muscle enolase could be appropriately used as antigen for the immunodiagnosis of malaria. ■

Published in: *Southeast Asian J Trop Med Public Health* 1999 (in press).

BLOOD-STAGE DYNAMICS AND CLINICAL IMPLICATIONS OF MIXED *PLASMODIUM VIVAX*-*PLASMODIUM FALCIPARUM* INFECTIONS

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n 1998, we reported that *Plasmodium falciparum* (*P.f.*) enolase was useful as the capture antigen for the immunodiagnosis of malaria. In the present study, we modified a fluorescence-ELISA for the diagnosis of malaria by applying yeast enolase or rabbit muscle enolase as antigen. Sera from 67 falciparum malaria patients and 15 vivax malaria patients were tested by this method. Positivity rates of the former were 82.1% against yeast enolase antigen and 90.5% against rabbit muscle enolase antigen, and those of the latter were 93.3% against both enolase antigens. Mean antibody titers (RFU values) of sera from falciparum and vivax malaria patients were significantly higher than those from healthy individuals. There was a significant correlation between anti-yeast and anti-rabbit muscle enolase antibody titers (RFU values) in the group of falciparum subjects ($r=0.401$, $P<0.001$). A significant correlation between RFU values against yeast enolase antigen and indirect fluorescent antibody titers against crude *P.f.* antigen in the same subjects was recognized ($r=0.518$, $P<0.001$). Longitudinal changes of RFU values against yeast enolase for the following 4 weeks after admission were also examined for sera from falciparum malaria patients. Patients with severe malaria showed increasing RFU values as the clinical course progressed. However, in the mild cases, each RFU value stayed unchanged during the course. We concluded that yeast and rabbit muscle enolase could be appropriately used as antigen for the immunodiagnosis of malaria. ■

We present a mathematical model of the blood-stage dynamics of mixed *Plasmodium vivax*-*Plasmodium falciparum* malaria infections in humans. The model reproduces features of such infections found in nature and suggests several phenomena that may merit clinical attention, including the potential recrudescence of a long-standing, low-level *P. falciparum* infection following a *P. vivax* infection or relapse and the capacity of an existing *P. vivax* infection to reduce the peak parasitemia of a *P. falciparum* superinfection. We simulate the administration of anti-malarial drugs, and illustrate some potential complications in treating mixed-species malaria infections. Notably, our model indicates that when a mixed-species infection is misdiagnosed as a single-species *P. vivax* infection, treatment for *P. vivax* can lead to a surge in *P. falciparum* parasitemia. ■

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Nuamtanong



Chatree Muennoo



Kasidis Visiadsuk



Surapol
Sa-nguankiat



Somchit Pubampen



Supaporn Naowarat



CURRENT RESEARCH ACTIVITIES

1. Monoclonal antibody-based competitive ELISA and indirect ELISA for immunodiagnosis of trichinosis.
2. The effects of *Trichinella spiralis* infection on renal functions in rats.
3. Health education for prevention of trichinellosis in Mae Hong Son Province.
4. Comparison of biochemical extract preparations of *Cysticercus cellulosae* by SDS-polyacrylamide gel electrophoresis and immunoblot technique.
5. Utilizing cystic fluid of *Taenia solium* metacestodes for IgG-ELISA in the detection of neurocysticercosis.
6. IgG-ELISA for detection of Bancroftian filariasis by using antigenic molecules of partial surface and excretory-secretory of *Dirofilaria immitis* adult worms.
7. Densitometric appearance of 24 kDa of albendazole-treated patients for gnathostomiasis, relationship between infectivity and eosinophilia.
8. Seasonal variation in the intensity of *Gnathostoma* larvae in swamp eels (*Fluta alba*) sold in a local market of Bangkok.
9. *Toxocara canis* antigens (excretory-secretory, crude extract, fractionate) for serodiagnosis of human toxocariasis.
10. *Angiostrongylus cantonensis* antigens for serodiagnosis of Angiostrongyliasis
 - : improvement of crude antigens.
 - : fractionated antigens.
11. Comparative protein patterns of the developmental stage of *Angiostrongylus cantonensis* by SDS-polyacrylamide gel electrophoresis and immunoblot.
12. Experimental infection of freshwater fish in Thailand with the infective stage of *Angiostrongylus* sp.
13. Angiostrongyliasis
 - : analysis of antigens of *Angiostrongylus costaricensis* adult worms versus IgG from infected patients with *Angiostrongylus cantonensis*.
14. Thermal effect on opisthorchid metacercariae in fish.
15. Studies on the efficacy of Thai traditional herbal medicines in the treatment of opisthorchiasis in hamsters.

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Abstracts

TOXOCARA AND GNATHOSTOMA AMONG STRAY CANINES IN BANGKOK

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Stomachs and intestines of 88 adult and 112 young stray dogs were obtained from the Rabies Control Subdivision, Bangkok, and examined especially for the presence of *Gnathostoma spinigerum* and *Toxocara canis*. Forty-five dogs were found positive for *T. canis* (overall prevalence 22.5%) but none was found infected with *G. spinigerum*. The prevalence of *T. canis* in young dogs was 37.5% (42 of 112) whereas in adult dogs it was only 3.4% (3 of 88). The total number of *T. canis* recovered from the 45 positive dogs was 272 (averaging 6.0 worms/dog). This includes 268 worms from 42 young dogs (averaging 6.4 worms/dog) and four worms from three adult dogs

(averaging 1.3 worms/dog). The average number of worms, according to sex and stage, per young dog were as follows: male worms 2.4 ± 3.5 (range 0-15), female worms 2.8 ± 3.5 (0-16), immature worms $1.2 (2.5 \pm 0.9)$, and all worms 6.4 ± 8.2 (1-34). The maximum number of worms per young dog was 34 while the minimum was one, and 35.7% (15/42) of these young dogs harbored only one worm. The body length of the recovered *T. canis* were as follows: males measuring 3.0-12.0 cm (averaging 7.1 ± 2.1 cm), females 4.1-18.2 cm (11.0 ± 4.1 cm), and immature worms 0.7 - 3.7 cm (2.1 ± 0.8 cm). ■

Published in: *Southeast Asian J Trop Med Public Health* 1998;29:744-7.

PRELIMINARY REPORT ON SOIL-TRANSMITTED HELMINTH EGGS FROM NIGHT SOIL SLUDGE AROUND THE BANGKOK METROPOLITAN AREA

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Night soil sludge samples from Nong Khaem Night Soil Treatment Plant were sent to the Department of Helminthology, Faculty of Tropical Medicine, for examination of helminthic materials. The specimens were examined by flotation method with sugar solution (sp.gr. 1.200) and the results revealed that 4 out of the 50 samples contained *Ascaris* and *Trichuris* eggs. Most *Ascaris* eggs detected from the sludge were alive (92.3%), their development varying from the one to the multicellular stage, and *Trichuris* eggs were degenerated and without the outer eggshell.

Nowadays, soil and stone for construction have been replaced by treated human excreta. It is quite possible that this change may effect the distribution of *Ascaris* infection in the urban community and lead to the recurrence of this particular intestinal helminthic infection among the urban population in the near future. ■

Published in: *J Trop Med Parasitol* 1998;21(1):46-7.

SOIL-TRANSMITTED HELMINTHS: SOURCE AND DISTRIBUTION OF THE INFECTIVE STAGES IN SOUTHERN THAILAND

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Soil-transmitted helminthiasis (STH) due to hookworm infection has been posing a public health problem in Thailand for several decades. A helminthiasis control program under the responsibility of the Communicable Disease Control Department, Ministry of Public Health, was introduced in 1971. The program consists of treatment with effective anthelmintic drugs, health education and improvement of environmental sanitation. Despite these efforts, the prevalence rate of hookworm infection in all population groups remains significant, with high reinfection rates in endemic areas. The transmission pattern was therefore re-evaluated among the groups at risk from the southern peninsular region of Thailand.

Examination of stool samples from primary school children of Tharuer Mitraparp 30 and Wat Pungsing School, Muang District, Nakhon Si Thammarat Province, demonstrated that 91.6% had soil-transmitted helminthic infections, of which 78.7% were hookworm infections. A survey of the infected pupils in each school revealed that most of them were from 5-6 groups of the same family name. After home visits and environmental observations in the village were carried out, many defective septic tanks were found. Liquid, and some solid particles, leaked from the tank through the holes or cracks of the body and/or the cover. The gradual leakage of sewage had prolonged the filling of the septic tank with waste.

Soil samples collected from the vicinity of the septic tanks and the latrines in the endemic area showed that 30.4% and 23.1% were contaminated with the infective stages of STH during the rainy and summer seasons, respectively. The number of eggs found during the wet season was 3 times that of the dry season. Most of the eggs found in the soil were alive (84.4%-97.1% - *Trichuris*; 84.6%-85.4% - *Ascaris*); only a few dead eggs (3.0%-15.6% - *Trichuris*; 15.4%-14.6% - *Ascaris*) were observed. About 38.1% of the soil from around contaminated households revealed positive findings throughout the year.

The present study suggests that wastes released from defective septic tanks are the main source of STH eggs and larvae in endemic areas. Man, household animals, vehicles and floods are important factors affecting the distribution of these infective stages. ■

Published in: *J Trop Med Parasitol* 1998;21(1):31-6.

OPISTHORCHIS VIVERRINI METACERCARIAE IN THAI FRESHWATER FISH

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Examination for metacercariae in freshwater fish, the common intermediate hosts of *Opisthorchis viverrini* was carried out during the period 1992-1996. The 4-year survey of fish from markets in 14 provinces revealed that metacercariae of *O. viverrini* were found in fish from Udon Thani, Sa Kaeo and Prachin Buri Provinces;

fish from Aranyaprathet district had the highest positive rates (25-28%). Fish from 12 provinces were found to be positive with heterophyid metacercariae, namely: *Haplorchis pumilio*, *H. taichui*, *H. yokogawai*, *Stellantchasmus falcatus*, *Centrocestus formosanus* and *Haplorchoides cahirinus*. It was also observed that the prevalence of *O. viverrini* metacercariae in fish has decreased markedly during the last 10 years. ■

Published in: *Southeast Asian J Trop Med Public Health* 1998;29(2):324-6.

PARADUJARDINIA HALICORIS (OWEN, 1833), A NEMATODE FROM THE STOMACH OF A SEA COW IN THE GULF OF THAILAND

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Twenty-seven male and 26 female roundworms were recovered from the stomach of a dugong (*Dugong dugon*) from Trang Province, Southern Thailand. The worms were kept in 70% alcohol and transported to the Department of Helminthology for study. The worm has three lips with interlabia, intestinal cecum and ventriculus. The male worm presents two spicules alate in the middle shaft, four pairs of precloacal papillae, two pairs of paraocals and two pairs of postcloacal papillae. After comparison with specimens borrowed from Queensland Museum, the nematode was ascertained to be *Paradujardinia halicoris*. ■

Published in: *Thai J Vet Med* 1998;28(3):49-56.

TRAINING OF PERSONNEL: THE REGIONAL TRAINING COURSE ON THE CONTROL OF INTESTINAL HELMINTHOSES WITH CONNECTION TO THE INTEGRATED PROGRAMME

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The regional training course on the control of intestinal helminthoses was initiated by the Asian Parasite Control Organization (APCO) to promote the concept of an Integrated Project (IP), implementing parasite control together with family planning and activities promoting nutritional status. It was primarily aimed at

training personnel from APCO member countries in order that they may serve as well-qualified trainers for the IP programme in their respective home countries. The course has been conducted annually since 1977 at the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, with 22 to 25 participants a year. They are invited through IP programmes from 11 participating countries, namely Bangladesh, Bhutan, Cambodia, Indonesia, Lao PDR, Malaysia, Nepal, the Philippines, Sri Lanka, Thailand and Vietnam; and occasionally from 8 other countries, namely Egypt, Guatemala, India, Japan, Mexico, Myanmar, Tanzania and Zambia. ■

IX International Congress of Parasitology ICOPA IX MakuHari Messe. 1998 Aug 24-28 Chiba, Japan: p.127-31.

PHYLOGENETIC RELATIONSHIPS AMONG THE THAI SPECIES OF PARAGONIMUS INFERRED FROM DNA SEQUENCES

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DNA sequences from the nuclear ribosomal second internal transcribed spacer (ITS2) and mitochondrial cytochrome c oxidase subunit I (COI) gene were obtained from species of lungflukes (genus *Paragonimus*) from Thailand and other countries. The sequences were used to investigate relationships among the Thai species and those from elsewhere. Of the Thai species, *P. macrorchis* and *P. heterotremus* are phylogenetically very distinct. *Paragonimus harinasutai* is related to members of the *P. ohirai* group which occur elsewhere in E. Asia. This relationship is not one that would be suspected on the basis of

morphology. *Paragonimus siamensis* and *P. westermanni* are closely related to one another and share some morphological features. This work is an important step towards recognizing groupings within the genus *Paragonimus* and establishing the basis for a taxonomic revision. ■

IX International Congress of Parasitology ICOPA IX MakuHari Messe. 1998 Aug 24-28 Chiba, Japan: p.643.

GNATHOSTOME INFECTION IN SWAMP EELS, *FLUTA ALBA*, IN CENTRAL THAILAND

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To investigate the distribution of gnathostome worms in central Thailand, the infective larvae of *Gnathostoma* spp. were examined from the flesh and liver of swamp eels, *Fluta alba*. Seven hundred and eighty-eight eels were purchased from markets in 11 provinces; Ang Thong (30), Ayutthaya (36), Chachoengsao (30), Lop Buri (30), Nakhon Nayok (437), Pathum Thani (30), Prachin Buri (48), Ratchaburi (53), Saraburi (30), Samut Prakan (30) and Suphan Buri (34). The highest rate

of gnathostome infection was observed in swamp eels from Nakhon Nayok (68.7%). The infection rates in Ayutthaya, Ang Thong, Prachin Buri, Ratchaburi, Saraburi and Lop Buri were 33.3%, 26.7%, 25.0%, 18.9%, 13.3% and 10.0% respectively. Gnathostome larvae were not found in swamp eels from Chachoengsao, Pathum Thani, Samut Prakan and Suphan Buri. Among the 9,573 larvae recovered, almost all were advanced third stage larvae of *G. spinigerum*, except one larva from Nakhon Nayok and two larvae from Ratchaburi which were identified as advanced third stage larvae of *G. vietnamicum* and *G. hispidum* respectively. This study is the first report of swamp eels as natural intermediate hosts of *G. vietnamicum* and *G. hispidum*. ■

Published in: *Southeast Asian J Trop Med Public Health* 1998;29(1):144-7.

STRONGYLOIDES STERCORALIS INFECTION AND CHRONOLOGICAL CHANGES OF OTHER SOIL-TRANSMITTED HELMINTHIASIS IN THE ENDEMIC AREA OF SOUTHERN THAILAND

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A field survey was conducted in 4 primary schools in Nakhon Si Thammarat Province, Southern Thailand. By Sasa modified Harada-Mori cultivation method, 1.8% of the schoolchildren were found to be infected with *Strongyloides stercoralis*, and 25.1% with hookworm infection. By Kato's thick smear method, the overall prevalence of soil-transmitted helminths was 46.8%, being *Trichuris trichiura* 28.5%, hookworm 18.0%, and *Ascaris lumbricoides* 5.7%. Fecal examination, performed by Kato's thick smear and culture method, indicated that the

prevalence of hookworm infection was 26.9%. The prevalence in the present study was very much lower than many previous reports in the past decade. This may indicate partial success of the parasite control project in Thailand by mass treatment, improving sanitation and personal hygiene of the people in the endemic area.

In light infection with *Trichuris*, albendazole administered at a dosage of 200 mg daily for 3 days showed a 48.7% cure rate. When mebendazole was given at 100 mg twice daily for 3 days, its effectiveness was 88.5%. A lower cure rate was obtained (70.0%) in moderate to heavy infection. ■

Presented at: the 21st APCO Parasitologists' Meeting. 1999 Jul 21-23 Tokyo, Japan.

EFFECT OF MEBENDAZOLE ON *TRICHURIS TRICHIURA* MORPHOLOGY

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Fecal examinations of primary schoolchildren in Nakhon Si Thammarat Province were performed by Kato's thick smear method. Treatment with mebendazole 100 mg x 2 x 3 was given to moderate and heavy trichuriasis cases. Three weeks later, 7 out of 10 treated children were cured, giving a cure rate of 70.0%. Daily expelled worms from each individual child from day 1 to day 7 were 0%, 6.7%, 18.0%, 40.4%, 28.0%, 4.5% and 2.4% respectively. The worms' sex ratio was M:F = 1:1.17.

Daily-collected *Trichuris trichiura* adults from a moderately infected case were preserved and processed for observation of significant changes due to the given drug. Four types of abnormalities in the muscular part were

observed. They were Type 1- shrunken or folded esophagus; Type 2- dislodged esophagus, Type 3- degeneration at the anterior tip; and Type 4- slim or thin esophagus. Over 30% of worms collected from the first and second bowel movement had a normal muscular esophagus. Most of the worms (95%) collected at day 5 after treatment had a degenerated esophagus. Degeneration of stichocytes occurred in treated worms from day 2. However, there was no relation between abnormalities of the anterior muscular part and degeneration of the posterior stichosomal part.

In hematoxylin and eosin cross-sectioned slides, there was distinct destruction and fragmentation of stichocytic cells after treatment with mebendazole. ■

Presented at: The 21st APCO Parasitologists' Meeting. 1999 Jul 21-23 Tokyo, Japan.

ANGIOSTRONGYLIASIS: ANALYSIS OF ANTIGENS OF *ANGIOSTRONGYLUS COSTARICENSIS* ADULT WORMS VERSUS IgG FROM INFECTED PATIENTS WITH *ANGIOSTRONGYLUS CANTONENSIS*

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The possibility of cross-reactivity was previously investigated by indirect ELISA with sera from *Angiostrongylus cantonensis* infections, normal controls and *A. costaricensis* antigen. 5 µg/ml of crude antigen from both sexes of each species reacted with diluted serum samples (1:800) of each of 20 cases of angiostrongyliasis and normal controls, and further with anti-human IgG conjugate at 1:1,000. The mean absorbance values were evaluated as follows; normal controls showed a value of 0.033 using *A. costaricensis* antigen lower than (0.085) *A. cantonensis* antigen. Both mean values of angiostrongyliasis cases were rather close (0.491) using *A. costaricensis* antigen and the other antigen (0.518). The present study continued with a crude antigen of 13 *A. costaricensis* females and males. Serum samples were analyzed; 27 sera of angiostrongyliasis, 30 negative controls and 193 cases of other parasitic infections (91 cases of

nematodiasis; 45 cases of cestodiasis; 47 cases of trematodiasis and 10 cases of HIV) and 7 cases of other brain infections. This antigen was evaluated for ELISA with a concentration of 5 µg/ml, serum dilution 1:400 and anti-human IgG conjugate at 1:2,000. The test gave sensitivity and specificity at cut-off value 0.261; 92.59% and 73% respectively. The antigen was cross-reactive with 30 cases from 9 out of 10 different kinds of nematodiasis (gnathostomiasis, strongyloidiasis, ascariasis, hookworm infection, trichinosis, toxocariasis, trichuriasis, onchocercosis and *Wuchereria bancrofti* infections). Five cases from 3 out of 6 kinds of cestodiasis (neurocysticercosis, hydatidosis and *Hymenolepis nana* infections) and 18 cases of 4 out of 5 kinds of trematodiasis

(*Paragonimus heterotremus* infections, opisthorchiasis, schistosomiasis and fascioliasis). One case of another brain infection was observed. The crude antigen of *A. costaricensis* showed a high percentage sensitivity with serum antibodies of angiostrongyliasis cases. Low specificity of the test was observed by reactions of those serum antibodies with various kinds of antigenic molecules. This study provides baseline data for further immunodiagnosis of human angiostrongyliasis. ■

Presented at: Joint International Tropical Medicine Meeting 1999 and The Fifth Chamlong-Tranakchit Harinasuta Lecture. 1999 Aug 4-6 Bangkok, Thailand.

ANGIOSTRONGYLIASIS: POTENTIAL FRACTIONATED ANTIGENS OF *ANGIOSTRONGYLUS CANTONENSIS* ADULT WORMS FOR DIAGNOSIS USING ELISA

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Indirect enzyme-linked immunosorbent assay (ELISA) for IgG detection was established by fractionated antigens from gel filtration (Sephacryl S-200). The crude antigen from *Angiostrongylus cantonensis*, both female and male adult worms, had been extracted by distilled water and further sonicated. To evaluate indirect ELISA, serum samples were analyzed, 27 sera of angiostrongyliasis, 30 negative controls and 144 cases of other helminthiases (nematode infections, 71 cases; cestode infections, 41 cases; and trematode infections, 32 cases). Seven cases of other brain infections were included in the test. Four peaks of crude antigen were obtainable and the antigen AcP2 showed the best discrimination, superior to

the other three peaks. The AcP2 was evaluated for ELISA with a concentration of 5 µg/ml, serum dilution 1:400 and anti-human IgG conjugate 1:2,000 for which the test gave sensitivity, specificity, positive and negative predictive values at cut-off value 0.266; 96.3%, 96.53%, 83.87% and 99.29% respectively. The antigen was crossreactive with antibodies from a total of five cases of trichinellosis (2/9), trichuriasis (1/6), schistosomiasis (1/6) and fascioliasis (1/5). The AcP2 of adult worms of *A. cantonensis* was shown to be superior in IgG-ELISA in determining human angiostrongyliasis. ■

Presented at: Joint International Tropical Medicine Meeting 1999 and The Fifth Chamlong-Tranakchit Harinasuta Lecture. 1999 Aug 4-6 Bangkok, Thailand.

SINGLE-DOSE ALBENDAZOLE AND MEBENDAZOLE FOR THE TREATMENT OF TRICHURIASIS IN NAKHON SI THAMMARAT

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The efficacy of a single-dose 400 mg tablet of albendazole and a 500 mg tablet of mebendazole were evaluated against trichuriasis in children at Wat Saplang primary school, Tambon Tangpoon, Chalerm Phrakiat District, Nakhon Si Thammarat, in southern Thailand. Stool samples were examined by quantitative cellophane-covered thick smear technique. Of the 302 children examined, 169 (56.0%) were positive for helminth ova. These consist of 35.8% (108/302) *Trichuris trichiura*. 24.5% (74/302) hookworm and 1.6% (5/302) *Ascaris lumbricoides*. The 108 trichuriasis children were divided

into two groups and were treated with either drug. Stool samples were re-examined twenty-one days post-treatment. The results revealed that treatment with a single dose of 400 mg albendazole gave a 32.7% cure rate and a 61.4% egg reduction rate. Treatment with 500 mg mebendazole yielded a cure rate and an egg reduction rate of 28.3% and 78.8%, respectively. ■

Published in: *Mahidol J* 1999;6(1):1-3.

IgG- AND IgG4-DETECTED ANTIGENS OF *DIROFILARIA IMMITIS* ADULT WORMS FOR BANCROFTIAN FILARIASIS BY ENZYME-LINKED IMMUNOELECTROTRANSFER BLOT

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In Thailand, *Wuchereria bancrofti* filariasis has persisted along the border between Thailand and Myanmar, its dynamic distribution caused by infected transmigrants between neighboring countries, and the availability of susceptible mosquito vectors. The *Dirofilaria immitis* adult worm was used as a source of antigens, excretory-secretory (ES) and partial surface extracts, to detect human filariasis. ES products showed several stained bands with Coomassie brilliant blue ranging from 14.5-93 kDa and mostly being glycoproteins as shown by concurrent reaction with Concanavalin A, except those at 18, 16 and 14.5 kDa which stained only with Coomassie brilliant blue. Surface proteins of 33.5-91.5 kDa were stained

with Coomassie brilliant blue and showed smear bands with Concanavalin A. By enzyme-linked immunoelectrotransfer blot, Bancroftian filariasis sera gave specific reactions with glycoprotein ES antigens at MW 20.5 kDa against anti-human IgG. A prominent band of 18 kDa appeared consistently with the IgG4-ES antigen system. Surface extracts reacting with IgG and IgG4 were considered to be unsuitable as antibodies from all cases of filariasis as we could not detect any bands. ■

Presented at: Joint International Tropical Medicine Meeting 1999 and The Fifth Chamlong-Tranakchit Harinasuta Lecture. 1999 Aug 4-6 Bangkok, Thailand.

PREVALENCE AND INTENSITY OF SOIL-TRANSMITTED HELMINTHS IN VILLAGES WITH CLUSTERED HOUSING AND DISPERSED HOUSING, NAKHON SI THAMMARAT PROVINCE

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Prevalence and intensity of soil-transmitted helminthic (STH) infections were studied in Tarue Village where the houses were clustered, and in Pung Sing Village where the houses were dispersed. Both villages are located in the same tambon of Muang district, Nakhon Si Thammarat Province. The study was carried out during the year 1996, and the quantitative cellophane-covered thick smear technique was employed to examine the stools for helminth eggs. The results showed that the prevalence of STH infections in Tarue Village was 79.9% with the prevalence of hookworm, *Trichuris trichiura*, and *Ascaris lumbricoides* infections being 53.5%, 64.4% and 14% respectively. The corresponding values for Pung Sing Village were 50.9%, 36.6%, 36% and 5.5%, respectively.

Results from Tarue Village revealed that the intensity of infection (light, moderate and heavy) was 67.9%, 22.2%, and 9.9%, 59.8%, 28.6%, and 11.6%, 60.3%, 24.1%, and 15.5% for hookworm, *Trichuris*, and *Ascaris*, respectively. The corresponding values for Pung Sing village were 94.6%, 4.2%, and 1.2%, 92.7%, 4.9%, and 2.4% and 72%, 20%, and 8%, respectively. ■

Published in: *J Trop Med Parasitol* 1998;21(1):40-3.

PREVALENCE AND INTENSITY OF SOIL-TRANSMITTED HELMINTHOSES IN TWO VILLAGES THREE YEARS AFTER A ONE-YEAR CONTROL PROGRAMME

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A one-year comparative control programme of soil-transmitted helminthoses (STH) using a combination of drug treatment and primary health care (PHC) intervention was conducted in two villages, i.e. Pung Sing (control village: only drug treatment) and Paruhas (experimental village: chemotherapy and PHC) in Nakhon Si Thammarat Province, Southern Thailand. The effectiveness of the programme was evaluated according to the prevalence and intensity of infection after one year of implementation of the programme, and three years after the completion of the programme. The infection rates of

STH in Pung Sing Village at the beginning of the control programme were as follows: overall prevalence 83.0%, hookworm 68.6%, *Trichuris* 60.4% and *Ascaris* 17.5%. The corresponding values for Paruhas Village were 80.0%, 49.6%, 62.1% and 12.5%, respectively. After the one-year control programme, the prevalence of STH in Pung Sing Village decreased to 60.4%, with hookworm 38.2%, *Trichuris* 43.0% and *Ascaris* 6.7%. The corresponding values for Paruhas Village were 50.4%, 12.5%, 44.3% and 3.0%, respectively. Three years after the completion of the programme, however, the prevalence of the infections in Pung Sing increased to 80.4% with hookworm 66.8%, *Trichuris* 65.3% and *Ascaris* 14.2%, in which the corresponding values for Paruhas Village were 68.3%, 20.2%, 56.7%, and 23.1%, respectively.

In Pung Sing Village, the prevalence of heavy hookworm infections at the beginning of the programme was 15.2%. It decreased to 6.2% at the end of the one-year programme, and increased to 18.0% three years thereafter. For trichuriasis, the statistics were 11.9%, 0% and 10.5%, respectively. In Paruhas Village, the prevalence of heavy hookworm infection at the beginning of the programme was 6.3%. It decreased to 0% at the end of the programme, and finally increased to 5.3% after three years. For trichuriasis, the statistics were 13.1%, 1.6% and 9.2%, respectively. For ascariasis, the number of heavily infected cases was too low for a quantitative evaluation. ■

Published in: J Trop Med Parasitol 1998;21(1):11-5.

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Panasoponkul



Sampas Nicharat



Raweewan Suwanich



Yudthana Samung



Samrerng
Prommongkol



Nuchthathip
Rodphadung



CURRENT RESEARCH ACTIVITIES

The research conducted in the Department of Medical Entomology involves both basic and applied knowledge applicable to controlling vectors of tropical diseases, especially mosquito-borne diseases. Other insects and arthropods of medical importance such as house flies, sand flies, cockroaches, fleas, ticks and mites are also studied in various aspects.

Laboratory colonies of different strains of vector mosquito species of *Anopheles*, *Aedes*, *Culex*, and *Mansonia* are continuously maintained in the insectarium for further use. The filarial parasite, *Brugia pahangi*, is also maintained in the reservoir host.

Study of the biology and ecology of mosquito vectors of malaria at Amphoe Suan Pung, Ratchaburi Province, i.e. *Anopheles minimus*, *An. maculatus*, *An. dirus*, and *An. aconitus* are conducted. The infection rate of malaria parasites, vector capability, and susceptibility to insecticides are also studied in each mosquito species. The baseline data obtained from this study will be used in the study of their species complex and malaria control in the study area.

The vectors of Japanese encephalitis, *Culex tritaeniorhynchus*, *Cx. gelidus*, *Cx. fuscocephala*, and that of dengue hemorrhagic fever, *Aedes aegypti* and *Ae. albopictus*, are studied for their ecology and vector potential. The species complex of these mosquitoes from various locations in Thailand are also investigated by enzymatic studies.

Effective controls of mosquito vectors are directed both in laboratory and field trials. The efficacy of chemical insecticides, insect growth regulator and chemosterilant are evaluated against the vectors. Studies on the development of insect resistance to these chemicals are also conducted. Non-polluting control methods, such as the use of medicinal plants, are tested. The use of insecticide-impregnated bed-nets and blankets (permethrin, etofenprox), especially for malaria control, has been introduced. Mosquito resistance to permethrin- and etofenprox-impregnated bed-nets studies are conducted in the laboratory to assess the impact on mosquito vectors.

The research project on “*Anopheles minimus* Species A complex in Thailand and their impact on malaria control” by S Sucharit, N Komalamisra, K Surathinth, and C Apiwathnasorn. (*J Trop Med Parasitol* 1997;20(2):57-67) received the Best Research Work 1998 Award by the National Research Council of Thailand.

Moreover, the Department of Medical Entomology acts as a reference center on mosquito vectors in Thailand through the establishment of the Mosquito Museum Annex and a project on computer aided management and service of biological museums. The Department also provides academic consultation, especially on mosquito-borne diseases and their control measures, and also services in the detection of filarial parasites, identification of mosquitoes and other medically important insects and arthropods.



Abstracts

PHYTOCHEMICAL EFFECTS OF *SAPINDUS RARAK* (SOAPBERRY) EXTRACTS AGAINST THREE SPECIES OF MOSQUITO VECTORS

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There are many serious drawbacks in the use of synthetic insecticides for vector control and alternative means of control are needed. Besides the adverse environmental effects, most major vectors have become physiologically resistant to many of these compounds. These factors have created the need for environmentally safe, degradable and target-specific insecticides against mosquitoes. The search for such compounds has been directed extensively at the plant kingdom and a number of questions about their performance

remain unanswered. This paper reports the efficiency of some Thai medicinal plants on mosquito vectors.

The effects of 12 phytochemical plants were tested against 3 species of mosquito vectors, *Aedes aegypti*, *Ae. albopictus* and *Culex quinquefasciatus*. The *Sapindus rarak* (soapberry) was found to be the most promising. The soapberry was extracted by 2 common solvents, distilled water and 95% ethanol with 24 hours maceration. Both extracts were tested against early 4th instar larvae. In all cases, exposure was for 24 hr, after which the larvae or pupae were transferred to clean water and examined periodically until all were dead or had emerged.

The LC_{50} values of water extract against *Ae. aegypti*, *Ae. albopictus* and *Cx. quinquefasciatus* were 379.28, 395.15 and 471.93 mg/l, whereas the alcohol extract values were 708.87, 761.82 and 876.41 mg/l, respectively. The former extract exhibited 2 times more toxicity than the latter, while both of them rendered the greatest activity against *Ae. aegypti*. The main effect was produced in the pupal stage of all tested mosquitoes, which suggested that the soapberry expressed the action of a juvenile hormone type. It is doubtless that the soapberry provides some type of new compound for vector control which is friendly to the environment. ■



LARVICIDAL EFFECT OF YAM BEAN (*PACHYRRHIZUS EROSUS*) EXTRACTS AGAINST *AEDES AEGYPTI*

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Part from the threat arising from insecticide resistance and environmental pollution, the search for safer and non-selective insecticides from phytochemical plants is one of interest for research in vector control. With the innovation of appropriate technology, this may be one of a plea for the stepwise progress of ecotoxicology and vector control. This paper reported the larvicidal activity of yam bean extracts against *Aedes aegypti*.

Larvicidal activity was dependent on parts of the plant, types of solvent extract and maceration time. Seed

water extract exhibited the best LC₅₀ values of 169.31, 180.75 and 194.15 mg/l at 24, 48 and 72 hours in maceration respectively, while for 95% ethanol extract were 411.28, 416.79 and 554.41 mg/l respectively at 24, 48 and 72 hours consequently. Based on the LC₅₀ values, it was clear that 24 hours' maceration showed the best LC₅₀. Therefore overnight could be recommended for maceration both in water and 95% ethanol.

No larvicidal effect of leaf water extract was observed, whereas 95% ethanol extract showed a greater effect. However, it was not economical for field use in larval control, since the LC₅₀ values were very high, in the region of 1353.21, 1543.17 and 3644.87 mg/l at 24, 48 and 72 hours in maceration. ■

SURFACE TOPOGRAPHY OF EGGS UNDER SEM AND METAPHASE KARYOTYPES OF *AEDES TOGOI* AND *TOXORHYNCHITES SPLENDENS* (DIPTERA: CULICIDAE)

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The eggs of *Aedes togoi* and *Toxorhynchites splendens* are described by means of scanning electron microscopy (SEM) and compared with other species within the genus reported in previous studies. *Ae. togoi* differs from other aedine species in that it has a sausage-shaped egg with the anterior or head-end obviously broader; exochorionic sculpture varies, i.e., penta-, hexa- or polygonal reticulum with approximately 2-12 small, irregular tubercles in each reticula; bi-radiate micropyle with polygonal, smooth collar outer ring, radially raised border of inner ring, irregular rim of micropylar disc, prominent cleft between micropylar disc and inner ring. *Tx. splendens* differed from other species in that it has a patternless arrangement without primarily hexagonal symmetry of

large outer chorionic tubercles. Metaphase karyotypes of both species consist of 3 submetacentric pairs (2n = 6). No heteromorphic chromosome was found in tissues from testis and ovary. Chromosome I was the shortest and chromosome III the longest. In *Ae. togoi*, the ovary chromosomes were shorter than the testis chromosomes, i.e., chromosome I 4.64 ± 0.87 μm and 6.52 ± 0.77 μm; chromosome II 6.15 ± 0.89 μm and 8.80 ± 0.78 μm; chromosome III 7.18 ± 1.13 μm and 9.78 ± 1.02 μm, from ovaries and testes, respectively, while these were reversed in *Tx. splendens* i.e., chromosome I 7.08 ± 1.60 μm and 6.41 ± 1.73 μm; chromosome II 9.54 ± 2.15 μm and 8.32 ± 1.82 μm; chromosome III 9.54 ± 2.15 μm and 9.52 ± 2.40 μm, from ovaries and testes, respectively. ■

Published in : *J Trop Med Parasitology* 1998;21(2):28-36.

INTERSPECIFIC HYBRIDIZATION AMONG *ANOPHELES BARBIROSTRIS*, *AN. CAMPESTRIS* AND *AN. DONALDI* (DIPTERA: CULICIDAE)

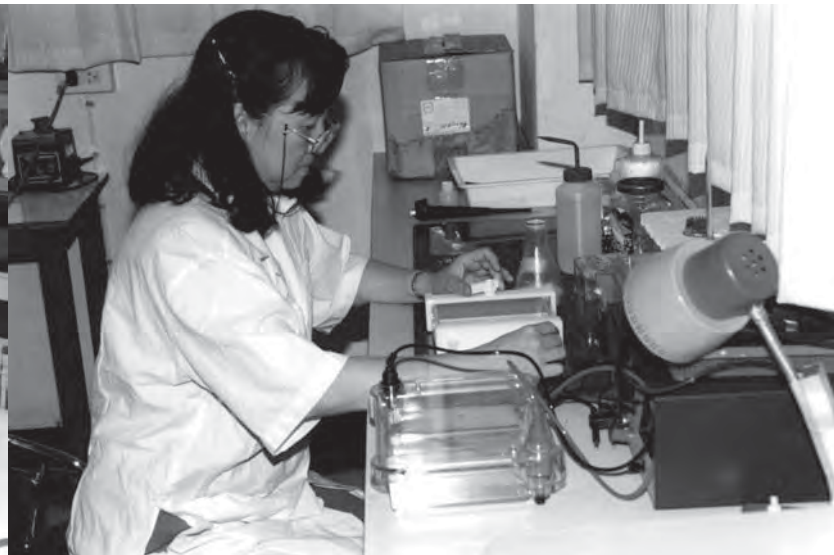
**Atchariya Jitpakdi¹,
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Crossing experiments among three member species of the *Anopheles barbirostris* species group, viz., *An. barbirostris*, *An. campestris* and *An. donaldi* were done by artificial mating in order to determine the genetic relationship. On comparison of the F1 hybrids and those of their parent species as the control, differences in embryonation, hatchability and viability were observed. The viability of F1 hybrids with high larval and pupal mortalities, producing sex distortion of adults, and the F1 hybrids' salivary gland chromosomes showed various degrees of asynapsis, suggesting that these three morphological species exhibited entire reproductive isolation. ■

Published in: *J Trop Med Parasitol* 1998;21(2):22-7.



ISOENZYME STUDY AND HYBRIDIZATION OF TWO FORMS OF *ANOPHELES SINENSIS* (DIPTERA: CULICIDAE) IN NORTHERN THAILAND

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The screening of ten isoenzymes of two forms of *Anopheles sinensis*, Form A and B, using electrophoretic gels revealed that Est-5⁹⁶ allele was the marker in both the 4th larva and adult female of *An. sinensis* Form B, whereas it was lacking in Form A. Hybridization tests of the two *sinensis* forms were done by induced copulation. The results of crosses indicated that they were genetically compatible, providing viable progeny and completely synaptic polytene chromosomes. ■

Published in: *Southeast Asian J Trop Med Public Health* 1998;29(4):84-8.

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The main responsibilities of the Department of Microbiology and Immunology include teaching and training, research, laboratory services and academic consultations.

TEACHING AND TRAINING

Several international courses at the postgraduate level, in microbiology and immunology including core subjects, elective and advanced courses are offered to the students of the D.T.M. & H. as well as M.Sc. and Ph.D. in Tropical Medicine. The Department also shares teaching of microbiology and immunology in other courses of Mahidol University and other universities and institutions. Several students elect to work for their thesis towards the M.Sc./Ph.D. degrees in various laboratories of the Department each year. Short courses on microbiology and immunology subjects are given periodically.

CURRENT RESEARCH ACTIVITIES

The current research activities of the Department involve studies on biology, molecular biology and immunology of infectious agents/diseases, particularly those causing problems in tropical areas, with the ultimate aims of 1) development of simple, rapid, specific, sensitive, cost-effective and practical diagnostic methods for use in remote areas and for the self-reliance of the country; 2) identification of potential protective antigens for vaccine development; 3) understanding of host responses and immunity; and 4) acquisition of and acquaintance with modern technologies, eg. genetic analysis of bacterial pathogens for epidemiological study. Further details are given below:

Sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting have been used for identification of the specific antigens of various pathogens including *Opisthorchis viverrini*, *Paragonimus heterotremus*, *Trichinella spiralis*, *Strongyloides stercoralis*, *Gnathostoma spinigerum*, *Entameba histolytica*, *Plasmodium falciparum* and *P. vivax*, *Leptospira*, etc. Successful identification of the specific antigens of these pathogens lead to the development of a more simple, rapid, sensitive and specific immunodiagnostic methods for patients suffering from these diseases. For example, in human gnathostomiasis, a 24 kDa specific diagnostic component of *G. spinigerum* was further purified from the crude extract by column chromatography. For affinity chromatography, the antigen used in the plate/membrane enzyme-linked immunosorbent assay (ELISA) gave 100% sensitivity and specificity for the disease. Attempts to produce the antigen either by recombinant DNA technology or anti-idiotypic antibodies are underway.

Specific polyclonal and/or monoclonal antibodies against various parasitic helminths, protozoa, bacteria and their toxins and viruses including *Opisthorchis viverrini*, *Paragonimus heterotremus*, *Schistosoma mekongi*, *Trichinella spiralis*, *Gnathostoma spinigerum*, *Entameba histolytica*, *Plasmodium falciparum* and *P. vivax*; bacteria or their toxins including *Bordetella pertussis*, *Vibrio cholerae* O:1 and O:139, *Salmonella*, enterotoxigenic *E. coli*, enterohemorrhagic *E. coli*, verocytotoxins (VT-I and VT-II), *Leptospira*, *Shigella*, *Rickettsia*, Japanese encephalitis virus and respiratory syncytial virus have been produced in our laboratory for detection of the pathogens/diagnosis of diseases caused by them in clinical specimens and/or contaminated food and environmental samples. The monoclonal antibodies produced against the whole cells, somatic and/or excretory-secretory antigens of these pathogens have been tested for their analytical as well as diagnostic sensitivity and specificity. Development of simple, specific, sensitive, rapid and cost-



effective methods which are of practical use in remote areas, such as the conventional or dot-blot ELISA, immuno-colloidal gold and/or the dip-stick techniques, as well as the use of immunomagnetic separation for higher sensitivity of detection of the pathogens have been carried out.

Additional work includes the application of DNA technology, e.g. development of DNA probes, PCR technology as well as other modern technology for the detection of several pathogens, e.g. *Paragonimus*, *Entamoeba*, *Plasmodium*, *Salmonella*, *Vibrio cholerae*, *Shigella*, *Bordetella pertussis*, dengue and respiratory syncytial viruses, etc. from clinical specimens and/or foods. DNA manipulations have been used for genetical analyses of various pathogens, eg. *Trichinella*, *Vibrio cholerae*.

Protective activities of various antigens such as frimbriae, hemagglutinin, procholeraenoid and lipopolysaccharide of a bacterial pathogen, *Vibrio cholerae*, associated with liposome adjuvant, are also studied. It was shown that oral immunization by the combination of these components provides strong local immunity against the bacterium. Phase I and II trials of the oral cholera vaccines, both against *V. cholerae* O:1, for tolerability and immunogenicity have been successful. A clinical trial on the protective role in volunteers and a field trial of the oral cholera vaccine are planned.

Studies on *E. histolytica* revealed that its genome organization consists of at least a circular supercoiled-like and linear DNA molecules that behave like yeast chromosomes. There was no evidence of chromosome rearrangement in association with drug resistance. The mechanism of metronidazole resistance in *E. histolytica* involved a marked increase in superoxide dismutase, whereas pyruvate:ferredoxin oxidoreductase was not decreased. A monoclonal antibody specific against *E. histolytica*, conjugated with red phycoerythrin (R-PE), was used successfully for the detection of trophozoites in human fecal samples. An immunotoxin (IT) consisting of a monoclonal antibody against pyruvate ferredoxin oxidoreductase of *E. histolytica* (EhPFORMAb) and the toxic moiety of the plant toxin ricin A (RA) is potent in inhibiting proliferation of the organism, and therefore, the IT would be one approach for future immunotherapy for invasive amebiasis.

Other areas of research activities on bacterial infections include diarrhea caused by *Campylobacter jejuni* and *E. coli*, anaerobic bacterial infections, non-gonococcal urethritis and heparinase detection in facultative and anaerobic bacteria. An antimicrobial susceptibility test was done by modified Kirby-Bauer's method to suit the small number of pathogens isolated each day. Surveillance of nosocomial infections for the control of hospital infections is also being investigated.

The study of nonfermentative gram-negative aerobic bacteria, to find a simpler and faster diagnostic scheme, is continuing for the development of an identification method that can be used in any hospital laboratory.

The Leptospirosis Unit is collaborating with Khon Kaen University in an epidemiology study of leptospirosis among cattle and rodents.

A more specific immunofluorescent technique has been developed to diagnose scrub typhus, and it is being evaluated with clinical samples in the Bangkok Hospital for Tropical Diseases and other hospitals, in order to replace the Weil-Felix test for routine laboratory service next year.

Parts of these research works are being carried out in collaboration with various international universities and institutions, i.e. the Department of Microbiology, Institute of Basic Medical Sciences, University of Tsukuba; the Institute of Tropical Medicine, Nagasaki University; the Department of Parasitology, University of Tokyo; the Department of Medical Technology, University of Okayama; the Research Institute, International Medical Center of Japan; the National Institute of Infectious Diseases, Tokyo, Japan; the Department of Microbiology and Immunology, Faculty of Medicine, Monash University, Melbourne, Australia; the Department of Microbiology and Immunology, Faculty of Medicine, University of Adelaide, Adelaide, Australia; the Queensland Institute of Medical Research and the University of Queensland, Australia; the Institute for Clinical Research in Tropical Medicine, Hanoi, Vietnam; the University of Vienna and the University of Innsbruck, Austria; the University of Stellenbosch, South Africa; the International Centre for Diarrhoeal Disease Research, Bangladesh; etc.

SCIENTIFIC AWARDS

In 1999, the staff of the Department received two distinguished scientific awards. The “**1999 Outstanding Scientist Award**” was given by the Foundation for the Promotion of Science and Technology, under the patronage of His Majesty the King, to **Professor Wanpen Chaicumpa** for her achievement in immunology.

The “**Best Research Work in Chemistry and Pharmaceutical Science Award**” was given by the National Research Council, Ministry of Science, Technology and Environment, Thailand to the study on “the Development of Oral Vaccine against Cholera” by **Professor Wanpen Chaicumpa and her colleagues**, i.e. Manas Chongsa-nguan, Thareerat Kalambaheti, Yuwaporn Sakolvaree, Potjane Srimanote, Pramuan Tapchaisri, Yuvadee Mahakunkijcharoen, Emsri Pongponratn, Urai Chaisri, Rujiporn Prateepasen, Jiraporn Limpananont, Polrat Wilairat and Sornchai Looreesuwan.



Abstracts

LOW CD8⁺ T LYMPHOCYTE RESPONSE TO *P. FALCIPARUM* CIRCUMSPOROZOITE PROTEIN IN NATURALLY-EXPOSED ENDEMIC POPULATIONS

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Cytotoxic T lymphocytes (CTL) specific for epitope(s) within the circumsporozoite (CS) protein of the malaria sporozoite have been shown to play an important role in protective immunity against murine malaria. Human CTLs against the potential carboxyl terminal region of 7G8 *P. falciparum* CS protein (Pf7G8CS 368-390) were determined in thirty-six falciparum malaria patients and 10 healthy controls. Four of 36 individuals and none of the healthy controls developed Pf7G8CS 368-390 specific CTL activity. The CTL activity was antigen-specific and CD8⁺T cell dependent. Although low CTL

response has been determined, the study seems to indicate that there was a correlation between initial parasitemia and the specific Pf7G8CS 368-390 CTL activity. The correlation between such CTL activity and anti-R32tet32 antibody levels among individuals with previous malaria experiences was found, which was in contrast to those among individuals with recent malaria infection. All these 4 positive CTL individuals had at least two episodes of clinical malaria, while all 25 individuals who were first exposed to malaria could not be found to have such a specific CTL response. These results showed that individuals with a history of natural endemic exposure to *P. falciparum* sporozoites developed a low specific CTL response to Pf7G8CS 368-390 and recent sporozoite exposure might be a prerequisite for the generation of such a CS protein specific CTL response. ■

Published in: Southeast Asian J Trop Med Public Health 1999 (in press).



CD4⁺ AND CD8⁺ T LYMPHOCYTE RESPONSES TO ZIDOVUDINE TREATMENT IN HIV PATIENTS

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The degree of CD4⁺ T cell depletion is currently the most important laboratory finding taken into consideration when recommendations are made regarding therapy with anti-retroviral drugs. It is commonly believed that the efficacy of zidovudine (ZDV) in treating HIV induced disease may be due to an increase in CD4⁺ T lymphocytes or a slowing of the loss of CD4⁺ T lymphocytes. We investigated the responses of CD4⁺ and CD8⁺ T cells in AIDS, symptomatic and asymptomatic HIV patients receiving ZDV, and controls without receiving ZDV before treatment and during a six month follow-up period. It was shown that the percentage and the number of CD4⁺

T cells and CD4⁺/CD8⁺ ratio was correlated in this study. In addition, the percentage and the number of CD4⁺ T cells and CD4⁺/CD8⁺ ratio in all AIDS cases was lower than that in asymptomatic and symptomatic HIV patients at the base-line. All AIDS patients had CD4⁺ T cell counts less than 200 cell/mm³ (16 to 199 cells/mm³) and the percentage of CD4⁺ T cells less than 14% (1 to 13%). ZDV therapy in AIDS patients did not show a beneficial increment of CD4⁺ T lymphocytes after six-month follow-up. Only a transient increment of CD4⁺ T cells was observed in the first month of treatment and it subsequently declined. A tendency for increment of CD4⁺ T cells was also found in symptomatic HIV patients after ZDV administration; however, too few subjects (n=2) limited statistical analysis in this group. A fluctuation of CD4⁺ T lymphocytes was observed in one asymptomatic HIV patient receiving ZDV throughout the study, reflecting drug toxicity, while the significant decline of CD4⁺ T lymphocytes was noted in asymptomatic HIV patients without ZDV at sixth month follow-up (p=0.025). The findings of CD8⁺ T cell counts were not conclusive. The percentages of CD4⁺ and CD8⁺ T cell and CD4⁺/CD8⁺ ratio in all HIV infected patients were not significantly different during the follow-up period compared with the base-line (p>0.1, p>0.2 and p>0.2, respectively). The incidence of neutropenia in patients receiving ZDV was significantly higher than those without ZDV, especially in AIDS patients. Therefore, the use of CD4⁺ T cell counts as the marker for monitoring the efficacy of ZDV requires the careful consideration of ZDV adverse effects. However, the limited number of patients studied with complete follow-up might cause non-conclusive results. More HIV patients should be included and long-term follow-up should be made in order to evaluate the benefits or the adverse effects of ZDV. ■

Manuscript in preparation for publication.

INDIRECT HEMAGGLUTINATION TEST USING MONOCLONAL ANTIBODY-AFFINITY PURIFIED ANTIGENS FOR DIAGNOSIS OF HUMAN PARAGONIMIASIS DUE TO *PARAGONIMUS HETEROTREMUS*

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An indirect hemagglutination test (IHA) using antigens purified by monoclonal antibody-affinity chromatography was developed for the diagnosis of human paragonimiasis caused by *Paragonimus heterotremus*. Sera from patients with paragonimiasis (n=30) were evaluated, along with sera from other parasitic infections (n=92), pulmonary tuberculosis (n=18) and healthy controls (n=30). The sensitivity, specificity as well as positive and negative predictive values of the IHA, calculated at the prevalence of disease at 17.6%, were all 100%. ■

This study was supported by the National Research Council of Thailand.

Published in: Trop Med Intern Health 1998;3:57-9.

RAPID DETECTION OF CHOLERA CAUSED BY *VIBRIO CHOLERAE* O139

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Hybridomas secreting specific monoclonal antibodies (MAs) to *Vibrio cholerae* serogroup O139 were produced. Six monoclones (hybridomas) secreting MAb specific only to lipopolysaccharide of *V. cholerae* O139 strains and which did not cross-react to 137 strains of other enteric microorganisms were obtained. These clones were designated 12F5-G11, 12F5-G2, 15F5-H5, 5B9-F8, 14C9-D2, and 6D2-D8. The immunoglobulin (Ig) heavy chain isotypes secreted by these clones were IgG2b, IgG2b, IgG2b, IgM, IgG2b, and IgG3, respectively. Clone 12F5-G11 was selected for mass production of MAb, which was used as a detection reagent in the antigen detection assay for diagnosis of cholera caused by *V. cholerae* O139, and this assay was compared with the conventional bacterial isolation method. Five batches of rectal swab cultures in alkaline-peptone water were collected from 6,497 patients with watery diarrhea. These were 6,310 patients admitted to Bamrasnaradura Infectious Diseases Hospital, 16 patients from Krung Thon Hospital, 78 patients from Bangkok Children's Hospital, 19 patients from Karen

refugee camps, and 74 Indian patients from the National Institute of Cholera and Enteric Diseases, Calcutta, India. The *V. cholerae* O139 isolations from the rectal swab cultures and the antigen detection assay (i.e., the MAb-based dot-blot ELISA) were performed by different persons of different laboratories, and the results were revealed after all specimens had been tested. Of the 6,497 samples tested, dot-blot ELISA correctly identified 42 of 42 *V. cholerae* O139-positive samples and gave a result of positive for three samples which were culture negative for *V. cholerae* O139. The diagnostic sensitivity, specificity, and efficacy of the dot-blot ELISA were 100%, 99.95%, and 99.26%, respectively. The ELISA is easy to perform and relatively inexpensive. It can test multiple samples at a single time, does not require special equipment, and does not produce great quantities of contaminated waste. Most of all, it reduces the diagnostic time from at least 2 days for bacterial isolation to less than 90 min. The assay is recommended as a rapid screening test of cholera cases caused by *V. cholerae* O139. ■

This work was supported by BIOTEC, NSTDA.

Published in: J Clin Microbiol 1998;36:3595-600.

IMMUNOGENICITY AND PROTECTIVE ROLE OF THREE FORMULATIONS OF ORAL CHOLERA VACCINE

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Three formulations of oral cholera vaccine were compared with respect to their immunogenicity and protective capacity in a rat ileal loop model. Eight-week-old Wistar rats were divided into five groups. The first group received orally vaccine A consisting of liposome-associated *V. cholerae* lipopolysaccharide, fimbriae and procho-leragenoid, whereas the rats of groups 2 and 3 received oral vaccines B and C consisting of heat-killed fimbriated and non-fimbriated whole cell *V. cholerae*, respectively. Rats of groups 4 and 5 were controls that received orally liposomes alone and normal saline solution,

respectively. It was found that vaccine A elicited stronger immune responses to all three *V. cholerae* antigens. The antibody responses were detected in both serum and intestinal lavage samples. Vaccine B elicited only modest serum and intestinal responses to *V. cholerae* fimbriae (anti-F). No detectable immune response was found in rats of group 3 immunized with vaccine C. Rats immunized with vaccines A and B had a similar order of magnitude of numbers of vibrios adhering to their intestinal mucosa. These numbers were fewer than those associated with the intestinal tissues of control rats of groups 4 and 5 by about two orders of magnitude. Although without any detectable immune response, rats of group 3 that were immunized with vaccine showed some reduction in the number of vibrios associated with their intestinal mucosa. The number of vibrios recovered from the intestinal segments of rats of all treatment groups was in the order group 1 = 2 < 4 = 5. Electronmicrography also revealed patches of vibrio colonization on the mucosa of rats of groups 3, 4 and 5. These features were not found in the groups vaccinated with vaccines A and B. The inhibition of vibrio colonization afforded by the vaccines was biotype- and serotype-non-specific. The results suggest that heat-killed whole cell fimbriated *V. cholerae* may be an alternative vaccine preparation to the liposome-associated refined antigen vaccine at a lower cost. ■

This work was supported by WHO, SEARO through the Ministry of Public Health, Thailand.

Published in : Vaccine 1998;16:201-7.

IMMUNOGENICITY OF LIPOSOME-ASSOCIATED AND REFINED ANTIGEN ORAL CHOLERA VACCINES IN THAI VOLUNTEERS

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A mixture of *Vibrio cholerae* antigens made up of crude fimbrial extract, lipopolysaccharide and procho-leragenoid was administered orally to Thai volunteers either as free antigen or associated with liposomes. All vaccinees and controls were administered in three doses given at 14-day intervals. Nine volunteers received liposome-associated vaccine and 7 received free vaccine. Liposomes without antigens were given to 8 volunteers and 7 volunteers received 5% NaHCO₃ solution alone. Both vaccines had 100% immunogenicity as determined by serum vibriocidal antibody responses. Liposomes were shown by indirect ELISA to localize the immune response against lipopolysaccharide and fimbriae to the intestinal mucosa. Vaccinees given liposome-

associated antigens had a higher rate of antigen-specific antibody response than did individuals who had received free antigens. The vaccines induced intestinal antibodies of IgM and/or IgA isotypes, but not IgG antibody. ■

This work was supported by WHO, SEARO through the Ministry of Public Health, Thailand.

Published in : Vaccine 1998;16:678-84.

DETECTION OF *SALMONELLA* CONTAMINATION IN FOOD SAMPLES BY DOT-ELISA, DNA AMPLIFICATION AND BACTERIAL CULTURE

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A dot-blot enzyme-linked immunosorbent assay (dot-ELISA) employing a genus *Salmonella* specific monoclonal antibody (MAb) was used for detection of the bacteria in food samples in comparison with the conventional culture method and DNA amplification. Among the 200 chicken and pork samples (100 each) tested, 9% and 33%, 7% and 20% and 7% and 23% were positive for salmonellae by dot-ELISA, culture method and DNA amplification, respectively. Statistical analyses revealed that the sensitivity, specificity, efficacy, and positive and negative predictive values of the detection of *Salmonella* in the food samples by dot-ELISA compared with the culture method were 93.33%, 91.76%, 92%, 66.66% and 98.73%, respectively. Comparison of the DNA amplification and culture methods revealed the sensitivity, specificity, efficacy, and positive and negative predictive values of 100%,

91.58%, 92%, 65.21% and 100%, respectively. The dot-ELISA and the DNA amplification results were in better agreement when the two assays were compared. The sensitivity, specificity, efficacy, positive and negative predictive values of the dot-ELISA compared with the DNA amplification were 91.3%, 100%, 98%, 100% and 97.5%, respectively. In this study, it was found that the dot-ELISA is rapid, simple, sensitive, and specific at low cost with a limited amount of infectious waste to be disposed of and offers another advantage, in that it detects only the smooth LPS of *Salmonella* which implies the possible presence of the virulent organisms. ■

Financially supported in part by BIOTEC, NSTDA, Ministry of Science, Technology and Environment, Thailand.

Published in: *Asian Pac J Allergy Immunol* 1999;17:41-51.

MONOCLONAL ANTIBODIES PRODUCTION SPECIFIC TO VITELLIN AND VITELLOGENIN OF GIANT TIGER PRAWN *PENAEUS MONODON*

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Monoclonal antibodies specific to *Penaeus monodon* vitellin and vitellogenin were produced using crude ovarian extract from gravid *P. monodon* ovaries. After immunization and fusion of the mouse spleen cells with P3X myeloma, hybridomas were selected by indirect immunoperoxidase ELISA against *P. monodon* ovarian extract, followed by dot-blotting against native and denatured proteins from ovarian extract, female hemolymph and male hemolymph. Four hybridoma clones producing antibodies (PMV - 11, 15, 22 and 64) were identified. They bound with ovarian extract proteins and with female hemolymph, but not with male hemolymph. One antibody (PMV-64) bound with both native and denatured proteins. Using Western blot analysis of ovarian extract separated by PAGE, all four monoclonal antibodies bound with the same lipoglycoprotein band. Using

Western blot analysis of proteins separated by SDS-PAGE, PMV-64 antibody bound with MW 80 and 83 kD proteins in ovarian extract, and with MW 83 and 200 kD proteins in female hemolymph, respectively. All four monoclonal antibodies belong to the IgG1 subisotype. ■

Published in: *Inver Reproduc Develop* 1999;35:9-17.

DETECTION OF *ESCHERICHIA COLI* O157 ANTIGEN AND SHIGA-LIKE TOXINS IN CLINICAL SPECIMENS USING MONOCLONAL ANTIBODIES

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Hybridomas secreting monoclonal antibodies (MAbs) to lipopolysaccharide (LPS) of *E. coli* O157 and A- and B-subunits of Shigatoxin-1 (Stx-1) and Shigatoxin-2 (Stx-2) were produced. Mono-epitope specificities of the MAbs were screened by heterologous antigens and homologous antigens. The MAbs, namely MAb to O157 LPS and MAbs to A- and B-subunits of Stx-1 and Stx-2 were used in a dot-blot ELISA for the detection of their respective antigens in stool samples collected from patients with diarrhea. The MAb-based dot-blot ELISA, when performed in double-blind manner, could correctly identify 5 samples of patients with *E. coli* O157 infections, while the tests were negative for samples collected from patients with diarrhea caused by other enteric pathogens. The membrane ELISA is easy to perform and relatively inexpensive compared with

the culture and DNA amplification methods. It offers a relatively rapid turn-around time (90 minutes), can test multi-samples at a single time, does not require special equipment, and does not produce large quantities of contaminated waste. Most of all, the test, using a cocktail of MAbs to A- and B-subunits of both toxins, offers advantages in detection of their respective antigen(s) in clinical specimens of patients infected with non-O157 Shiga toxin-producing bacteria. ■

This work was financially supported by the Thailand Research Fund, Thailand and Grant in Aid, Japan.

CHARACTERIZATION OF A PUTATIVE VIRULENCE ISLAND IN THE CHROMOSOME OF UROPATHOGENIC *ESCHERICHIA COLI* POSSESSING A GENE ENCODING A UROPATHOGENIC-SPECIFIC PROTEIN

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This study was initiated to search for a homologue of the *Vibrio cholerae* zot gene in uropathogenic *Escherichia coli* (UPEC) using a specific DNA probe. The faint signal obtained at low stringency with some UPEC strains associated with prostatitis cases prompted us to examine UPEC strains by PCR using primers designed from the conserved regions of the proteins of the zot group of putative NTPases containing the classical NTP binding motif. This led to the discovery of a DNA fragment in UPEC strains which hybridized with a probe designed from the PCR. Further analysis of this DNA fragment revealed an ORF which was designated as uropathogenic specific protein (Usp). The gene encoding Usp was 1,038 bp long and codes for 346 amino acids with an appropriate SD sequence. Upstream and downstream analysis of Usp revealed motifs of prokaryotic consensus promoters and 3 small ORFs with SDs and ribosome binding sites transcribed in the same direction of Usp. The proximity of these sets

of genes in a specific area of the bacterial chromosome resembling a block of genes preferentially associated with UPEC, coupled with the presence of a motif matching that of a Tn3 transposon family, leads us to believe that this could be an hitherto unknown pathogenicity island. ■

Accepted for publication in Microbial Pathogenesis, 2000.

PREVALENCE OF ANTIBODIES TO *SCHISTOSOMA MEKONGI* AMONG INHABITANTS OF THE HIGH RISK AREA OF THAILAND

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Serum samples were collected from 339 inhabitants of Ubon Ratchathani Province, Thailand, which is located in the immediate vicinity of Kong island, Laos, where *schistosomiasis mekongi* is endemic (group 1). The samples were subjected to indirect- and dot-blot ELISA using *Schistosoma* heterophile substance, *i.e.* keyhole limpet hemocyanin (KLH), as the antigen. Thirty-five serum samples of residents of Bangkok, which is a low risk area for blood fluke infection, were tested concurrently. It was found that 10 of 339 samples of group 1 revealed KLH-indirect ELISA optical densities higher than the uppermost limit of samples from group 2. These 10 serum samples were negative when tested by indirect ELISA using affinity purified, specific antigen of *Trichinella spiralis*. The finding implied that the high optical densities found when the samples were tested by the KLH-indirect ELISA were not incited by *T. spiralis*, the infection which had been known to stimulate antibodies reactive also to the KLH. All sera of both groups 1 and 2 were negative when tested against KLH and specific *T. spiralis* antigen in dot-blot ELISA. Careful evaluation of the ages and occupations of the 10 individuals of group 1 revealed that their age range was 18 to 72 years old, and 50% or more of them were farmers with high chances of exposure to water, where the *S. mekongi* infective cercariae might be present. Moreover, none of the 10 individuals denied swimming in the Mekong River. Thus, the possibility exists that high optical densities of the 10 serum samples in the KLH-ELISA might be due to naturally exposed to/undetected (light) infection by *Schistosoma mekongi*. ■

This study was co-supported by the Thailand Research Fund, the National Research Council of Thailand, the Ministry of Public Health, Thailand, the National Centre for Biotechnology and Genetic Engineering, the National Science and Technology Development Agency, Ministry of Sciences, Technology and Environment, Thailand and the Faculty of Tropical Medicine, Mahidol University, Bangkok.

Submitted to: J Trop Med Hyg, 1999.

DIPSTICK ANTIGEN-CAPTURE ASSAY FOR DIAGNOSIS OF MALARIA

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A dipstick assay for detection of *P. vivax* blood stage antigen has been developed and tested sequentially in patients with vivax malaria. Using specific monoclonal antibody (MAb) McPV1 against *P. vivax* common blood stage antigens of 30 kD and 80 kD, the assay was able to detect as few as 5 parasites/10⁶ erythrocytes in *P. vivax* blood lysate. The assay was specific since it was positive only with *P. vivax* infected erythrocytes from vivax malaria patients and negative when erythrocytes from

healthy individuals and falciparum malaria cases were tested. The assay was positive for 89.2% of 234 vivax malaria cases before anti-malarial treatment proven by microscopic examination. On day 7, and 14 days after treatment, one of the follow-up cases that was proven negative by microscopic examination was positive by dipstick assay. The specificity of the test was 100%. ■

Manuscript in preparation for publication.

TRICHINELLA SPIRALIS-SPECIFIC MONOCLONAL ANTIBODIES AND AFFINITY-PURIFIED ANTIGEN-BASED DIAGNOSIS

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Hybridomas secreting monoclonal antibodies (MAbs) to *Trichinella spiralis* were produced. Myeloma cells were fused with splenocytes of a mouse immunized with excretory-secretory (E-S) antigen of infective larvae. A large percentage of growing hybrids secreted antibodies cross-reactive to many of 23 heterologous parasites tested. Only 6 monoclonal antibodies (designated 3F2, 5D1, 10F6, 11E4, 13D6 and 14D11) secreted MAbs specific to the E-S antigen and/or a crude extract (CE) of *T. spiralis* infective larvae. The 6 monoclonal antibodies secreted IgM, IgG3, IgM, IgG3, IgG3 and IgG3, respectively. Clone 5D1 was selected to mass produce MAbs which were then coupled to CNBr-activated Sepharose CL-4B to prepare an affinity-purified antigen. Dot-blot ELISA with either purified antigen or CE was evaluated. There were 17 patients with acute trichinellosis and 76 individuals convalescing from *T. spiralis* infection (group 1). Controls were 170 patients with parasitic infections other than trichinellosis (group 2) and 35 healthy parasite-free controls (group 3). CE-ELISA was positive in all group 1 patients. However, sera from many group 2 patients also were reactive (opisthorchiasis 44.2%, schistosomiasis 44%, gnathostomiasis 30%, paragonimiasis 28.6%, taeniasis 27.3%, strongyloidiasis 23.1% and hookworm infections

20%). Affinity-purified antigen was 100% specific, and all sera from group 2 and group 3 individuals tested negative. Although 74 of 76 patients (97.4%) with convalescing trichinellosis tested positive, sera from only 3 of 17 patients (17.6%) with acute *T. spiralis* were reactive. Thus, CE antigen is appropriate when sensitivity is needed, while purified antigen should be used when specificity is required. Dot-blot ELISA is easier to perform, more rapid and less expensive than indirect ELISA. Many samples can be assayed simultaneously, special equipment is not required, and results can be preserved for retrospective analysis. Dot-blot ELISA is therefore the method of choice for the rapid diagnosis of trichinellosis, particularly when more complex laboratory tests are unavailable. ■

This study was co-supported by the National Research Council of Thailand, the Faculty of Tropical Medicine, Mahidol University, the Government of Thailand Annual Budget and the National Centre of Genetic Engineering and Biotechnology, National Science and Technology Development Agency, Ministry of Science, Technology and Environment, Thailand.

Submitted to: Parasitol Intern, 1999.

SUBGROUP DETERMINATION OF RESPIRATORY SYNCYTIAL VIRUS BY RT-PCR

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PCR optimization for differentiation of RSV subgroup A (RT-PCR-1) and RSV subgroup B (RT-PCR-2) were developed. Various conditions of RT-PCR-1 and RT-PCR-2 were summarized. These methods are highly specific and sensitive to differentiate RSV subgroup A and RSV subgroup B from other respiratory viruses. ■

Published in: Southeast Asian J Trop Med Public Health 1998;29:751-7.

DIFFERENTIAL DIAGNOSIS OF SCHISTOSOMIASIS MEKONGI AND TRICHINELLOSIS IN HUMANS

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Antibodies incited by *Schistosoma* spp. in the infected individuals cross-react with a mollusk, *Megathura crenulata*, hemocyanin, namely keyhole limpet hemocyanin (KLH). As such, the KLH has been used as a heterophile antigen in the diagnosis of acute schistosomiasis or detection of antibodies to *Schistosoma* spp. in exposed individuals. However, the antibodies reactive to the KLH were also found in patients with trichinellosis. Thus, in the area where the two parasitic infections are concurrently endemic, the KLH-immunoassay is no longer appropriate. In this study, we have developed an indirect (plate) ELISA and, a more convenient version, a dot-blot (membrane) ELISA using the KLH and purified, specific antigen of *Trichinella spiralis* (APTAg) obtained from a monoclonal antibody-affinity column chromatography, for differential diagnosis of the two parasitic infections. Serum samples of patients with parasitologically confirmed trichinellosis were reactive to both antigens in both versions of ELISA while sera of patients with schistosomiasis mekongi were positive only to the KLH. Both ELISA were negative when used to test sera of normal controls and patients with gnathostomiasis, paragonimiasis and opisthorchiasis. ■

The study was co-supported by the National Research Council of Thailand, the Faculty of Tropical Medicine, Mahidol University, the Government of Thailand Annual Budget and the National Centre of Genetic Engineering and Biotechnology, National Science and Technology Development Agency, Ministry of Science, Technology and Environment, Thailand.

Submitted to: *Parasitol Intern*, 1999.

MONOCLONAL ANTIBODIES TO QUININE

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Monoclonal antibodies (MAbs) to quinine conjugated to a carrier protein were produced. Quinine was converted into a hemisuccinate prior to being covalently linked to bovine serum albumin (BSA) by reaction with N,N-disuccinimidyl carbonate (DSC). The coupling ratio of quinine-BSA was 13:1 calculated by spectrophotometry and 14:1 by calculation from quinine standard curve. This immunogen was used for both monoclonal antibody production and for indirect ELISA screening test. The specificity of quinine-BSA MAbs was examined by checking the cross-reactivity with BSA and

the structurally related antimalarial drug, mefloquine. Six MAbs belonging to IgG1 were obtained. These MAbs slightly reacted with mefloquine-BSA because of the closely related structure of mefloquine to quinine and a similar conjugate preparation procedure used for conjugation. One selected MAb against quinine-BSA, showed higher reactivity with blood samples from patients previously treated with quinine when compared with normal blood. This preliminary test indicated that MAbs obtained may be useful as the probe for detection of quinine in biological fluids. ■

Published in: *Southeast Asian J Trop Med Public Health* 1998;29(2):337-40.

MONOCLONAL ANTIBODIES SPECIFIC OF THE GENUS *LEPTOSPIRA*, PATHOGENIC SPECIES *INTERROGANS* AND *LEPTOSPIRA* LIPOPOLYSACCHARIDE AND THEIR APPLICATIONS IN DIAGNOSIS OF HUMAN LEPTOSPIROSIS BY AN ANTIGEN DETECTION ASSAY

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Diagnosis of leptospirosis is based primarily on either isolation of the pathogen from patient's specimen or demonstration of a rise in serum antibodies. The former is laborious, costly, and often unsuccessful. Demonstration of a rise in serum antibodies involves a microscopic agglutination test (MAT). This test has several drawbacks which limit its wide use in the developing part of the world where leptospirosis occurs more extensively. These include the requirements of maintaining a broad range of *Leptospira* serovars for live antigen preparations, a panel of serotyping antisera which are costly and not extensively available, and technical expertise, among many others. Thus, a better alternative diagnostic measure is needed. In this communication, hybridomas secreting monoclonal antibodies (MAbs) specific to all members of the genus *Leptospira* (genus specific) and those that are specific only to the pathogenic species, i.e. *interrogans* and *Leptospira* lipopolysaccharide have been produced. The MAbs were used as the detection reagents in an antigen detection assay for a specific diagnosis of acute leptospirosis. The test can also be used for evaluation of the efficacy of treatment as the assay became negative after successful treatment. ■

This work was financially supported in part by the Senior Researcher Award, BIOTEC, NSTDA, Thailand.

GENETIC ANALYSIS OF *TRICHINELLA SPIRALIS* THAI ISOLATES

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The gap genes within LSU rRNA of the individual infective larvae of human and pig *T. spiralis* of Thailand isolates were identified. Polymerase chain reaction was performed to increase DNA extracted from each larva of the parasite. Electrophoretic analysis of the PCR amplicons revealed that the length of the gap gene was less than 500 bp. PCR amplicons were ligated into pGEM®-T Easy vector and then transformed into *E. coli* JM 107. Recombinant clones were identified using *Lac* selection and then subjected to automatic DNA sequencing. It was found that the gap region was flanked by the consensus sequence CGAAAG, which have been implicated in gap processing or recognition site, at both termini. From sequencing data, the gap genes of the *T. spiralis* larvae of the human isolate could be divided into four different groups, and those of the pig isolate could be divided into three groups. Comparisons of the sequences of gap genes of the parasites of both isolates revealed that they were

genetically similar, both in length and in base sequences. Nevertheless, a difference in nucleotides at position 93 could be observed. There were many variables at this position in gap genes of the larvae of the pig isolate such as pig L₂, pig L₄₋₁₀ contained T, pig L₃ contained G and pig L₁ showed the deletion at the positions 93-95 whereas those of the human isolate showed consistency at the same position. ■

This work was financially supported in part by BIOTEC, NSTDA and the Faculty of Tropical Medicine, Mahidol University.

PURIFICATION OF SHIGA-LIKE TOXINS (VEROCYTOTOXINS) FROM ENTEROHEMORRHAGIC *ESCHERICHIA COLI* AND THE PRODUCTION OF SPECIFIC MONOCLONAL ANTIBODIES TO THE TOXINS

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Stx1 and Stx2 were purified by procedures consisting of ammonium sulfate fractionation, DEAE-Sepharose column chromatography, chromatofocusing column chromatography and FPLC. Both toxins showed toxicity to the Vero cells. About 0.87 pg of purified Stx1 caused a 50% cytopathic effect (CD₅₀) to the cells. The CD₅₀ of partially purified Stx1 and Stx2 obtained after DEAE-Sepharose column chromatographies (Stx1-IEC and Stx2-IEC) were 6.8 pg and 1.38 ng, respectively. It was shown that Stx2-IEC was less toxic to the Vero cells than the Stx1-IEC. Mouse MAbs against A- and B-subunits of both Stx1 and Stx2 were produced through hybridoma technology. Four hybridomas, namely clones 11E3G3 and 3C9D4 which produced MAbs specific to A- and B- subunits of Stx1 and 26E9F9 and 13D4D2 which produced MAbs specific to the A- and B- subunits of

Stx2, respectively were selected for use in the subsequent toxin neutralization assays. MAbs produced by the first three clones were IgG₁ while those MAbs from clone 13D4D2 was IgG_{2a}. MAbs secreted by each clone were tested for their neutralizing capability and ability to inhibit 100 CD₅₀ of these respective toxins. The results indicated that MAbs to B-subunit of both toxins conferred higher neutralizing capability to the respective holotoxins than the MAbs to the A-subunits and could completely inhibit the 100 CD₅₀ of respective toxin activities. The MAbs to A-subunit could only partially inhibit the activities of the toxins; however, they conferred synergistic toxin inhibitory effect when mixed with the MAbs to B-subunit. ■

This work was co-supported by the Thailand Research Fund; BIOTEC, NSTDA, and Grant in Aid, Japan.

DETECTION OF CYTOKINE IN DENGUE HEMORRHAGIC FEVER PATIENTS IN THAILAND

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The ELISA systems of BIOTRAK (Amersham) were used to detect cytokine levels in sera from clinically severe dengue patients in Nakorn Phanom, Northeastern Thailand in 1993. Interleukin-1β (IL-1β) was detected in 35.7% of dengue hemorrhagic fever (DHF) patients, while its positive rate in patients with pyrexia of unknown origin (PUO) and those of dengue type 1 virus (D1) infection were 5.3% and 6.3% respectively. On the other hand, patients infected with dengue virus type 2 (D2), type 3 (D3), or type 4 (D4) did not show detectable levels of IL-1β. Statistical analysis indicated the DHF patients possessed higher levels of IL-1β compared with D1-D4 virus infection, PUO, and control (P≤0.01). The highest level of IL-1β was

detected in a case on day 3 after admission, while lower levels were detected in another 3 patients. IL-6 was another detected in 50% of DHF cases, while its positive rates in PHO, D1, D2 and D3-4 infected cases were 36.8%, 6.3%, 25%, and 18.5%, respectively. Statistical analysis indicated that DHF patients possessed higher levels of IL-6 compared with other patients infected with D2, D3, D4, PUO and control (P≤0.01). However, the levels of IL-6 among DHF patients were in a similar range to PUO and D1-infected cases, although a single case of D2-infection possessed higher level of IL-6. In 4 cases, the IL-6 level was high on the first day and decreased on the third and fifth days. Our results showed that in dengue virus infection, cytokines could be released, either directly from monocytes and macrophages as a result of dengue virus infection, or after interaction between virus infected cells and immune cells. ■

This study was financially support by the Ministry of Education, Japan.

CLONAL DISSEMINATION OF *VIBRIO PARAHAEMOLYTICUS* DISPLAYING SIMILAR DNA FINGERPRINT BUT BELONGING TO TWO DIFFERENT SEROVARS (O3:K6 AND O4:K68) IN THAILAND AND INDIA

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Active surveillance of *Vibrio parahaemolyticus* infection among hospitalized patients in Calcutta, India, showed the appearance of the O4:K68 serovar for the first time in March 1998 alongside the continued predominant incidence of the O3:K6 serovar. Strains belonging to both these serovars have been reported to possess pandemic potential by virtue of their enhanced ability to cause diarrheal illness in different part of the world. The genomes of O3:k6 and O4:k68 strains isolated from two different countries, India and Thailand, were examined and compared by different molecular techniques to determine their relatedness. The O3:K6 and O4:K68 strains from Calcutta and Bangkok carried the *tdh* gene but none possessed the *trh* gene. Characterization of representative strains of these two serovars by ribotyping showed that all the isolates had an identical ribotype. Further, analysis by AP-PCR with two different sets of primers revealed complete identity between O3:K6 and O4:K68 *V. parahaemolyticus* clones isolated in Calcutta and in Thailand. Pulsed field gel electrophoresis performed with the same set of strains yielded near similar RFLP patterns for all the 9 strains of *V. parahaemolyticus* comprising the O3:K6 and O4:K68 isolates of India and Thailand.

Phylogenetic analysis of the *Not* I restriction fragment length polymorphism showed that the O3:K6 and O4:K68 strains from clinically different sources formed a cluster with 78% to 91% similarity, thus indicating a close genetic relationship between the two different serovars isolated during the same time-frame but from widely separate geographical regions. ■

Submitted for publication in Epidemiology and Infection.

PRODUCTION OF SPECIFIC MONOCLONAL ANTIBODIES AGAINST *OPISTHORCHIS VIVERRINI* EGG ANTIGENS

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Ten Balb/c mice were immunized with egg antigen of *Opisthorchis viverrini* (OvEAg). Three mice were selected as splenocyte donors for three cell fusions. The spleen cells of these immune mice were fused with P3x-63-Ag8 myeloma cells. A total of 5 hybridomas produced specific antibodies to the OvEAg. Hybrids so obtained produced antibodies which could be classified according to their tissue specificities into three groups. The first group of antibodies reacted weakly to the worm tegument, muscle and eggs while those belonging to the second group reacted strongly to all of the above tissues. The monoclonal antibodies of the third group gave a positive reaction only to the egg content and eggshell of *O. viverrini*. ■

This research was financially supported by Mahidol University Research Grant and BIOTEC, NSTDA, Ministry of Science, Technology and Environment, Thailand.

SEROGROUP- AND SEROTYPE-SPECIFIC HYBRIDOMAS TO *SHIGELLA* SPP. AND RAPID DIAGNOSIS OF SHIGELLOSIS

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Hybridoma technology was applied for the production of serogroup- and serotype-specific hybridomas to *Shigella* spp. To produce hybridomas secreting monoclonal antibodies (Mabs) against all serotypes of the four *Shigella* serogroups, 13 cell fusions were carried out and 349 hybridomas producing specific MAbs to various serotypes of *Shigella* spp. were obtained. Among them, monoclonal antibodies secreted by 13 monoclones namely: MAbSS1, MAbSS2, MAbSF1, MAbSF8, MAbSF11, MAbSF18, MAbSF19, MAbSF24, MAbSB2, MAbSB4, MAbSB5, MAbSB12, and MAbSD were selected for use as detection reagents to detect *Shigella* spp. in clinical specimens by MAb-based dot-blot ELISA. All secreted MABs gave the

typical reaction pattern of LPS. The specificities of these MABs were assessed by both indirect- and dot-blot ELISA against whole cell lysate (Ly) and lipopolysaccharide (LPS) antigens of 44 strains of *Shigella* of all 4 groups and 114 strains of other bacteria and *E. histolytica*. These selected monoclonal antibodies were used singly or appropriately combined into four sets of MABs preparations and they were used for detecting antigens of individual serogroups of *Shigella* spp. in the rectal-swab samples of 42 patients with invasive diarrhea admitted to the "108" Hospital, Hanoi, Vietnam. The diagnostic specificity, sensitivity, and efficacy of the dot-blot ELISA compared with the culture method were 86.9%, 52.6% and 71.4%, respectively, for detection of *S. flexneri* and 100%, 61.9% and 80.9%, respectively, for detection of *S. sonnei*. The kappa coefficient values indicated a good degree of agreement beyond chance of the dot-blot ELISA and the culture method. Detections of the *S. boydii* and *S. dysenteriae* in rectal swab samples by both bacterial culture and dot-blot ELISA using specific MABs to group C and group A, respectively, were negative. The 100% accuracy of the MAB-based dot-blot ELISA was calculatedly obtained. Thus, these 4 sets of MABs have a high potential for use in *Shigella* spp. detection from clinical samples, provided that the sensitivity of the assay is improved, for example, by increasing MAB concentrations. Besides offering simplicity, rapidity, cost-effectiveness and a lesser problem of contaminated waste disposal, the dot-blot ELISA also offers multisample analysis at one time. It is recommended as a rapid screening test for shigellosis diagnosis. No complicated and expensive equipment is needed to carry out the assay. Therefore, the test is suitable for use in field conditions, community hospitals, remote health centers, and epidemiological investigations and stations, e.g. refugee camps. ■

This work was financially supported by the Senior Researcher Award, BIOTEC, NSTDA, Ministry of Science, Technology and Environment, Thailand.

MIC DETERMINATION OF PENICILLIN AND OXACILLIN RESISTANT GRAM POSITIVE COCCI BY THE E-TEST

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Resistant staphylococci to methicillin and resistant *S. pneumoniae* to penicillin are important problems for treatment of serious infections. The MIC value is needed for adjusting or selecting proper drug treatment. Determination of the MIC is not available in the general bacteriology laboratory. Previous data available regarding resistant organisms were based on the disk diffusion test that lack a real MIC value. The resistant strains could be

low or highly resistant organisms which will be different for the antimicrobial administration plan.

We evaluated the MIC of 98 staphylococci and 100 streptococci strains found in clinical samples of patients in the Bangkok Hospital for Tropical Diseases, using the E-Test for oxacillin and penicillin. We found that 71.4% of *Streptococcus pneumoniae* were resistant to penicillin. There were 9/28 with the MIC of ≥ 2 microgram/ml and 11/28 were moderately resistant (MIC 0.12-1 $\mu\text{g/ml}$).

Resistance to penicillin was found among the group B streptococcus. There were 6/11 with low resistance (MIC >0.25 -2) and 1/11 with the MIC of 4 $\mu\text{g/ml}$.

All of the group D (non enterococci) were resistant to penicillin. Four out of 6 were inhibited by 0.5-2 $\mu\text{g/ml}$ and another 2 had a MIC of 3 and > 32 $\mu\text{g/ml}$, respectively.

There were some resistant alpha streptococci, 11/35 with a MIC 0.25-2 and 5/35 were ≥ 4 $\mu\text{g/ml}$.

Less than 10% of *Staphylococcus aureus* were MRSA (8/81), they are all highly resistant strains (the MIC > 256 $\mu\text{g/ml}$).

There were 29.4% MRSE found, 4/17 were highly resistant (MIC > 256) and 1/17 had a MIC of 16 $\mu\text{g/ml}$.

MRSA, MRSE, PRSP and resistant streptococci are real problems that we found by the E-Test, though the resistant Staphylococci were fewer than expected.

MIC should be measured for every serious infection in order to select the antimicrobial agent and adjust the proper dosage to be used. The E-Test is a practical test that can be used in the laboratory where the conventional MIC test is not available. Though the price of the test is very high, it will be justified in life-threatening infection. ■

This study was financially supported by Mahidol University Research Grant.

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EDUCATION

The Department of Protozoology is one of the 11 departments within the Faculty of Tropical Medicine, Mahidol University. It was one of the first 5 departments created at the beginning of the Faculty of Tropical Medicine in the year 1960. Its responsibilities are teaching, training, research and service in the field of medical protozoa.

Teaching

1. Regular courses

- 1.1 Diploma in Tropical Medicine and Hygiene (D.T.M.&H.)
 - 1.1.1 Core Subject TMPZ 501 : Protozoology
 - 1.1.2 Elective subject TMID 505 : Parasitology
- 1.2 Master of Science in Tropical Medicine (M.Sc. Trop. Med.) and Doctor of Philosophy in Tropical Medicine (Ph.D. Trop. Med.).
 - 1.2.1 Core Subject
 - TMID 512 : Tropical Medicine
 - 1.2.2 Elective Core Subject
 - TMID 503 : Medical Protozoology
 - TMID 516 : Practical Parasitology
 - 1.2.3 Free Elective
 - TMID 517 : Biochemistry of Parasites
 - TMID 518 : Advanced Parasitology
 - TMID 519 : Experimental Techniques in Parasitology
 - TMID 520 : Molecular Biology of Parasites
 - TMID 521 : Antiparasitic Agents

2. Other courses

The Department

- 2.1 In conjunction with some international organizations, has provided some international training courses.
- 2.2 Provides opportunities for both local and foreign medical personnel to train in special topics within the Department.
- 2.3 Teaches special topics in other universities.

Training Courses

1. Laboratory Diagnosis of AIDS-related Protozoa.
2. Workshop on Clinical and Laboratory Diagnostic Parasitology.

CURRENT RESEARCH ACTIVITIES

1. Study on DNA replication enzymes of *Plasmodium falciparum* as new chemotherapeutic targets against malaria.
2. Effects of DNA gyrase inhibitors on *Trichomonas vaginalis* in cultures.
3. Isolation and characterization of DNA topoisomerase II from *Trichomonas vaginalis*.
4. Toxoplasma antibody in the healthy Thai population.
5. Serological of *Toxoplasma gondii* antibody in HIV+ve and HIV -ve patients.
6. Inhibition of *Giardia intestinalis* and *Entamoeba histolytica* by medicinal plants.
7. Studies on ultrastructure of *Giardia intestinalis* trophozoites after exposure to drugs.
8. *Blastocystis hominis* in children with diarrhea in children's hospitals.
9. *In vitro* cultivation for *Cryptosporidium* spp.
10. Rapid detection of *Entamoeba histolytica* antibody.
11. Comparison of *Toxoplasma gondii* detection between in-house latex agglutination and commercial test.
12. Effects of DNA topoisomerase I inhibitors on *Trichomonas vaginalis in vitro*.

SERVICES

The Department of Protozoology provides the following services:

- I. Special techniques for diagnosis of protozoal diseases such as:
 1. Diagnosis of toxoplasmosis by using Dye-Test technique.
 2. Diagnosis of cryptosporidiasis, *Cyclospora* spp., microspora by special staining techniques.
 3. Identifying intestinal protozoa by nuclear staining.
- II. Provides protozoal specimens for teaching to other institutes when requested.

Abstracts

GAMETOCYTOCIDAL ACTIVITY OF PYRONARIDINE AND DNA TOPOISOMERASE II INHIBITORS AGAINST MULTIDRUG-RESISTANT *PLASMODIUM FALCIPARUM* IN VITRO

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Gametocytocidal activities of pyronaridine and DNA topoisomerase II inhibitors against two isolates of multidrug-resistant *Plasmodium falciparum*, KT1 and KT3 were determined. After sorbitol treatment, pure gametocyte cultures of *P. falciparum* containing mostly young gametocytes (stage II and III) obtained on day 11 were exposed to the drugs for 48 hours. The effect of the drugs on gametocyte development was assessed by counting gametocytes on day 15 of culture. Pyronaridine was the most effective gametocytocidal drug against *Plasmodium falciparum* isolates KT1 and KT3; with 50% inhibitory concentration of 6 and 20 nM, respectively.

Moreover, the 50% inhibitory concentration of pyronaridine was lower than that of primaquine, which is the only drug used to treat malaria patients harboring gametocytes. Prokaryotic (norfloxacin) and eukaryotic (amsacrine and etoposide) DNA topoisomerase II inhibitors were only effective against asexual but not sexual stages of the malaria parasites. Based on the results, pyronaridine has both schizontocidal and gametocytocidal activities against the human malaria parasite, *Plasmodium falciparum*. ■

This study was supported by the Thailand Research Fund.

Published in: Parasitology International (in press).

PARTIAL PURIFICATION OF DNA POLYMERASE FROM *PLASMODIUM FALCIPARUM* MITOCHONDRIA AND ITS SENSITIVITY TO INHIBITORS

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Mitochondria of chloroquine-resistant *Plasmodium falciparum* (K1 strain) were isolated from mature trophozoites by differential centrifugation. Cytochrome c reductase, mitochondrial marker enzyme, was employed to monitor the steps of mitochondria isolation. Partial purification of DNA polymerase from *P. falciparum* mitochondria was performed using fast protein liquid chromatography (FPLC). A single peak of DNA polymerase activity was found in the mitochondria extract. DNA polymerase of *P. falciparum* mitochondria was

characterized as a γ -like DNA polymerase based on its sensitivity to inhibitors aphidicolin, N-ethylmaleimide and 1- β -D-arabinofuranosyladenine-5'-triphosphate. It was, however, strongly resistant to dideoxy-thymidine-5'-triphosphate ($IC_{50} > 400$ mM) and differed in this aspect from the host homologue, possibly indicating structural differences between host and *P. falciparum* DNA polymerase γ . In addition, DNA polymerase of parasite mitochondria was also resistant to nucleotide analogues (S)-1-[3-hydroxy-2-phosphonylmethoxypropyl] adenine diphosphate and 9-[2-(phosphonylmethoxy)ethyl] adenine diphosphate ($IC_{50} > 1$ mM). ■

This study was supported by The Thailand Research Fund.

IN VITRO SENSITIVITY OF *TRICHOMONAS VAGINALIS* TO DNA TOPOISOMERASE II INHIBITORS

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Vaginal trichomoniasis is a highly prevalent sexually transmitted disease caused by a microaerophilic protozoan *Trichomonas vaginalis*. The disease is one of the most common sexually transmitted diseases and can augment the predisposition of individuals to human immunodeficiency virus (HIV) infection. Although the disease can be treated with metronidazole and related 5-nitroimidazole, cases of trichomonal vaginitis which are

refractory to standard treatment seem to be increasing. Clearly, new antitrichomonal agents are needed and DNA topoisomerase II may act as a new target for antitrichomonal agents. In this study, *in vitro* sensitivity of *Trichomonas vaginalis* to DNA topoisomerase II was investigated. Axenic culture of a local strain of *Trichomonas vaginalis* was performed. Both eukaryotic and prokaryotic DNA topoisomerase II inhibitors such as ellipticine, amsacrine and fluoroquinolones were tested for effectiveness against *Trichomonas vaginalis in vitro* compared with metronidazole. The result showed that *Trichomonas vaginalis* was sensitive to metronidazole under aerobic conditions. Minimal inhibition concentrations (MICs) of eukaryotic DNA topoisomerase II; ellipticine and amsacrine were 6.4 μ M and 64 μ M, respectively. The MICs of prokaryotic DNA topoisomerase II or DNA gyrase inhibitors; ciprofloxacin, ofloxacin and norfloxacin were 64, 960 and 1280 μ M, respectively. Based on the results, among DNA topoisomerase II inhibitors, ellipticine was the most effective drug against *Trichomonas vaginalis in vitro* whereas fluoroquinolones did not showed high antitrichomonal activity. ■

This study was funded by Mahidol University.

INHIBITORY EFFECTS OF 9-ANILINOACRIDINES ON *PLASMODIUM FALCIPARUM* GAMETOCYTES

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Cultures of *Plasmodium falciparum* gametocytes of stage II, III and IV were used to test the gametocytocidal activity of 9-anilinoacridines. After drug exposure for 48 hours, gametocytes were maintained without drug for another two days before thin films were prepared for parasite counting. Gametocytocidal activities of 13 analogs of 9-anilinoacridine were observed with 50% inhibitory concentrations in the range of 0.6 μ M to greater than 100 μ M. The most active compound was 1'-CH₂NMe₂-9-anilinoacridine. Anilinoacridine derivatives with 3,6-diamino substitution had reduced gametocytocidal activity in contrast to their enhancing effect against the asexual forms. Morphological abnormalities of gametocytes were observed following drug exposure. ■

This study was supported by the Thailand Research Fund.

TOXOPLASMA GONDII ANTIBODY IN PREGNANT WOMEN WITH AND WITHOUT HIV INFECTION

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One thousand, two hundred pregnant women were examined for *Toxoplasma gondii* antibody with the objectives of identifying the prevalence and risk factors of the disease. Using Sabin-Feldman Dye test, the prevalence of IgG to *T. gondii* was 13.2%. In this study 19 cases (1.6%) were anti-HIV seropositive. Between HIV-seropositive and HIV-seronegative pregnant women, antibody rates to *T. gondii* were 21.1% and 13.1%

respectively, however, statistical comparison could not be done due to the very few subjects in the former group (n=4).

Concerning the risk factors, among those who had no cat in their houses, the prevalence of *T. gondii* antibody was significantly different between under-cooked and properly-cooked meat consumers (19.5% and 9.6% odds ratio=2.28, 95% confidence interval). And when under-cooked meat consumers were excluded, the antibody to *T. gondii* between two groups (having and not-having a cat in the house) were also found to be significantly different (31.8% and 19.3%; odds ratio=1.96, 95% confidence interval).

In conclusion, consuming under-cooked meat and having a cat in the house are both risk factors of transmission of toxoplasmosis. Further study with more subjects in HIV-infected pregnant women who have antibody to *T. gondii*, will be helpful for confirmation of the difference with respect to the non HIV-infected group. ■

This study was funded by Mahidol University.

Published in: Southeast Asian J Trop Med Public Health 1998;29(2):383-6.

DIFFERENCE OF *TOXOPLASMA GONDII* ANTIBODIES BETWEEN THAI AND AUSTRIAN PREGNANT WOMEN

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Toxoplasma gondii IgG and IgM antibodies of Thai and Austrian pregnant women were studied, in the same laboratory unit, using the Sabin-Feldman Dye Test and ISAGA-IgM. In Thai pregnant women, IgG antibody was found in 21.7%; mostly the IgG titers were low and all were negative of IgM antibody. Conversely, in

Austrian pregnant women, IgG antibody was found in 30.0% with high titer, and there were 19 (6.3%) of cases positive for IgM antibody.

The seropositivity of *T. gondii* IgG antibody in Austrian pregnant women was significantly higher than in Thai ($p=0.02$) and the titers were much higher. Two possibilities are postulated to explain the data. It may be because Thai women were infected at a younger age than Austrian women, so they were in a chronic infection stage corresponding with their negativity of IgM antibody or it may be due to the difference in strain virulence of *T. gondii* from different parts of the world. ■

Published in: Southeast Asian J Trop Med Public Health 1999;30(1):38-41.

TOXOPLASMA GONDII ANTIBODY IN HIV INFECTED PATIENTS

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Toxoplasmosis in the immunocompromised host was not documented in Thailand until 1992 when HIV/AIDS infection became pandemic. Patients with toxoplasmic encephalitis and cerebral abscess were recorded, particularly from the northern part of the country. However, data on the prevalence of the disease in HIV/AIDS patients is not yet available. In this study we determined the prevalence of *T. gondii* antibody in HIV

patients. During a two-year period, 312 serum samples of which 190 were HIV positive, and the remaining samples were negative for HIV, were tested. In the HIV positive group, 44 samples (23.2%) were positive for toxoplasma IgG antibody, whilst in the HIV negative group 36 samples (29.5%) were positive. All antibody titers found were not higher than 1.64. There is no significant difference of toxoplasma IgG antibody in HIV positive and HIV negative patients ($p=0.25$). Among the HIV positive and *T. gondii* antibody positive group, 19 out of 44 patients (43.2%) had symptoms and signs of acute toxoplasmosis involving the eye and/or the central nervous system. Due to the high reactivation rate, we propose that all HIV infected patients should be tested for *T. gondii* antibody and primary prophylaxis should be considered in those with positive results. ■

This paper has been accepted for publication in J Med Assoc Thai.

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CURRENT ACTIVITIES

The Department is comprised of four units, namely, the Applied Malacology Unit, Environmental Medicine Research Unit, Environmental Toxicology Unit and Social and Economic Research Unit. Our development and research, teaching, training and service activities are as follows: Course work provides three tracks of Environmental Health, Medical Malacology and Social Medicine. The Department aims to teach the subjects that are related to environmental health problems, environmental toxicology, medically important vectors of diseases, ecology, social medicine and the epidemiology of tropical diseases. The target students are from the M.Sc., Ph.D. programs and the D.T.M & H. course of the Bangkok School of Tropical Medicine. The research aspect of the Department involves various kinds of concerns to its academic staff of the four units, for instance, in field research, there are environmental health impact assessment of development projects, industrial pollution, social and economic impacts of malaria, dengue hemorrhagic fever, liver fluke infection, AIDS, other human related disease risks, and disease vector studies. Laboratory research includes the development of diagnostic procedures for parasitic diseases and AIDS vaccine data-base management. Academic services are functions of Department staff, to cooperate with outside-department training programs, teaching, seminars, workshops, conferences and as facilitators. The Department also provides laboratory animals and specimens to students and researchers upon their request. The Toxicology Unit is well equipped and available to serve for identification and analysis of industrial and environmental toxicants.

CURRENT RESEARCH

1. FIELD RESEARCH

Mainly, research work is concerned with disease survey and reconnaissance of human behaviors, disease vectors, animal hosts of protozoa and parasitic diseases. Investigation of the biological mechanisms by which hazardous wastes from industrial and agricultural processes has also been conducted to assess human health and environmental impacts. The studies form parts of series as follows:

- A) Environmental health impact assessment for adverse effects of water resource development projects and water pollution.
- B) Epidemiology of vector-borne diseases, such as DHF and malaria, and snail-borne diseases such as schistosomiasis surveillance in development projects, such as Pak Mun Dam and Rasrisalai Dam Project.

- C) Industrial and agricultural wastes that produce hazards to man and the environment, such as how pesticide use affects the reproductive system of women farmers in the northeast of Thailand.
- D) Social and economic studies explore the relationship of man and tropical disease infection. Some research has developed sociological models to assist disease control programs, for example, liver fluke infection, malaria and dengue hemorrhagic fever control.

2. CLINICAL RESEARCH

In relation to HIV-1 vaccine trial and baseline data for a possible vaccine efficacy trial, there were several studies of a prospective cohort of injecting drug user (IDUs) to determine rates of successful followup, HIV-1 incidence, and risk factors for seroconversion, and to characterize infecting HIV-1 strains. Abstracts of the publications concerning clinical research appear in the following pages.

LABORATORY RESEARCH

Laboratory research comprises parasitology, microbiology and toxicology, such as (1) mass production of *Opisthorchis viverrini* material for use in related opisthorchiasis research, such as the production of specific monoclonal antibodies, immunodiagnostic methods for opisthorchiasis (in collaboration with the Department of Microbiology and Immunology); (2) immunity of *Schistosoma mekongi* infection: preparation of antigen from cercariae, schistosomulae and adult worms (in collaboration with the Department of Microbiology and Immunology); (3) detection of *Mycobacterium leprae* by polymerase chain reaction (PCR) using tissue samples from fresh frozen and paraffin embedded skin biopsies; and (4) maternal lead level detection in breast milk and cord blood in different locations.

TRAINING/WORKSHOPS

From time to time, the Department hosted visitors from all over the world in both visits and short training courses regarding tropical diseases. In the past year, we organized training courses in environmental management, for example, a training course on "Water Quality Control and Management" held in April 1999. THAITREM/UNEP/DANCED also supported a series of training workshops on industrial pollution prevention. This comprised 3 workshops namely 'Industrial Toxicants and Pollution Prevention' held in October 1998, 'Risk Assessment and Industrial Pollution Prevention' in May 1999 and 'Industrial Pollution Prevention' in June 1999. These three workshops provided solid information, case studies and technology for both academic and industrial sectors.



Abstracts

VIRAL LOAD AND CD4 CELL COUNT IN INJECTING DRUG USERS (IDUs) NEWLY INFECTED WITH HIV-1 SUBTYPES B' AND E, BANGKOK

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Objectives: To compare the early post-seroconversion course of infection with HIV-1 subtypes B' (Thai B) and E among IDUs followed in a prospective cohort study.

Methods: HIV testing was performed every 4 months. After an HIV-positive test result, blood was obtained at time 0, and at months 1, 4, 8, 12, etc. Incident HIV-1 strains were characterized by direct DNA sequencing of the C2-V3 *env* region, plasma viral load was determined by Roche Amplicor HIV-1 Monitor v.1.5 testing, and CD4/CD8 cell counts were determined by FACScan flow cytometry.

Results: Through 1998, 134 IDUs became HIV-1 infected; 127 specimens were available for analysis: 100 (79%) had subtype E, and 27 (21%) had B'. IDUs with E and B' had similar demographic and behavioral characteristics. Within 3 months of seroconversion, viral levels (copies/mL) were higher for subtype E than for B': geometric means of 46,000 vs. 22,000 ($p=0.04$) and medians of 53,000 vs. 16,000 ($p=0.003$), respectively. However, viral levels were similar 12 months after seroconversion: means of 37,000 and 20,000 ($p=0.1$) and medians of 46,000 and 26,000 ($p=0.2$), respectively. Mean CD4 counts (cells/ μ L) were similar for E and B' at all time points: 584 vs. 558 at 3 months ($p=0.7$) and 480 vs. 502 at 12 months ($p=0.7$), respectively.

Conclusion: The early post-infection viral levels were somewhat higher for subtype E than for B', but CD4 cell counts were similar at all time points. Continued follow-up of this cohort of IDUs will further define the clinical course of infection and response to treatment for HIV-1 subtypes B' and E. ■

This study was supported by the HIV/AIDS Collaboration (A Joint Activity of the Thailand Ministry of Public Health & the U.S. Centers for Disease Control and Prevention).

Published in: The Fifth International Congress on AIDS in Asia and the Pacific, Kuala Lumpur, 1999.

INCARCERATION AS A CONTINUING HIV RISK FACTOR AMONG INJECTING DRUG USERS (IDUs) IN BANGKOK

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Background: Bangkok experienced a very rapid spread of HIV among IDUs in 1988, followed by stable seroprevalence at approximately 30-40% with continued high incidence. Estimated incidence from a prospective cohort of IDUs attending 15 Bangkok Metropolitan Administration methadone clinics during 05/95-05/98 was 6.3 per 100 person-years at risk. Previous cross-sectional surveys have shown that having been incarcerated was significantly associated with being HIV seropositive, with odds ratios in the range of 2 to 3. We evaluated risk factors for incarceration among cohort enrollees.

Methods: HIV-negative IDUs were offered enrollment after informed consent; data were obtained from enrollment and follow-up questionnaires. HIV testing and counseling and interviews on demographics, drug use, and sexual behaviors were conducted at enrollment and scheduled every 4 months.

Results: Of 1,209 HIV-negative IDUs enrolled, 133 seroconverted through 12/98. A proportional hazard

model demonstrated factors associated ($p < 0.01$) with HIV infection in Bangkok IDUs include: daily injection of heroin (RR=2.4), daily injection of heroin plus sharing of equipment (RR=3.2), being incarcerated since last visit (RR=2.0), drug injection while being incarcerated since last visit (RR=4.5), and having an average monthly income of < 5,000 Baht (US\$ 140, RR=1.6). Sixty-five percent of cohort members had been incarcerated prior to enrollment, and 38% of cohort members were incarcerated at least once during follow-up. Factors associated with being incarcerated, using logistic regression, included: age < 25 years old (RR 2.3, 95% CI = 1.6 - 3.2, referent: age 40+ years), having secondary school education or less (RR = 1.5, 95% CI=1.1 - 2.1, referent: higher education), being in the methadone maintenance program (RR = 0.6, 95% CI = 0.4 - 0.8, referent: 45-day detoxification program), and daily use of heroin plus sharing drugs (RR = 3.1, 95% CI = 2.3 - 4.2, referent: no use).

Conclusions: Drug use while being incarcerated is a strong risk factor for the incidence of HIV infection in Bangkok IDUs. Frequent heroin injection and lower socio-economic status lead to a higher probability of being incarcerated. Additional measures are needed to reduce the risk of HIV transmission related to incarceration. ■

This study was supported by the HIV/AIDS Collaboration (A Joint Activity of the Thailand Ministry of Public Health & the U.S. Centers for Disease Control and Prevention).

Published in: The Fifth International Congress on AIDS in Asia and the Pacific, Kuala Lumpur, 1999.

HIGH HIV-1 INCIDENCE AMONG INJECTING DRUG USERS (IDUs) IN A VACCINE PREPARATION COHORT, BANGKOK, THAILAND

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Background: Despite drug abuse treatment, HIV education and counseling, and legal access to sterile injection equipment, HIV-1 transmission rates among Bangkok IDUs have remained high since 1988. To study the feasibility of conducting an HIV vaccine efficacy trial in this population, a prospective cohort was established to determine HIV incidence, rates of follow-up, risk factors for seroconversion, and characteristics of infecting HIV strains.

Methods: From May 1995 to December 1996, IDUs attending 15 Bangkok Metropolitan Administration drug treatment clinics were screened, and HIV-negative IDUs were offered enrollment, with informed consent, into the cohort. HIV testing and counseling and interviews on demographics, drug use, and sexual behaviors were conducted at enrollment and scheduled every four months. Most IDUs were treated with methadone. For HIV-1 seroconversions, infecting HIV-1 subtypes were determined by direct DNA sequencing of the C2-V3 *env* region.

Results: Of 3,643 IDUs screened, 30% were HIV-positive. Of 1,209 HIV-negative IDUs enrolled, 86% and 68% remained in the cohort at 12 and 24 months, respectively. Through December 1998, 133 IDUs had seroconverted after 2,308 person-years (PYs) of observation (incidence=5.8/100 PYs; 95% CI=4.8-6.8). Of 126 HIV-1 specimens available for sequencing, 99 (79%) were subtype E and 27 (21%) were subtype B' (Thai B). Factors associated with HIV seroconversion in a proportional hazard model were: daily injection of heroin (RR=2.4, 95%CI=1.4-4.0, referent: lesser frequency or no use), daily injection of heroin plus sharing of equipment (RR=3.2, 95% CI=1.8-5.8, referent: lesser frequency or no use), being incarcerated since last visit (RR=2.0, 95%CI=1.3-3.2, referent: not incarcerated) and drug injection while being incarcerated since last visit (RR=4.5, 95%CI=2.6-7.8, referent: not incarcerated), and having an average monthly income of <5,000 baht (US\$ 140, RR=1.6, 95%CI=1.1-2.2, referent: > 5,000 baht).

Conclusions: Bangkok IDUs remain at high risk for HIV despite active interventions. In response, a phase III efficacy trial of an HIV-1 vaccine (AIDSVAX™ B/E, VaxGen, USA) was started in this population in March 1999. ■

This study was supported by the HIV/AIDS Collaboration (A Joint Activity of the Thailand Ministry of Public Health & the U.S. Centers for Disease Control and Prevention).

Published in: The Fifth International Congress on AIDS in Asia and the Pacific, Kuala Lumpur, 1999.

COST-EFFECTIVENESS ANALYSIS OF LAMBDAHALOTHRIIN-TREATED NETS FOR MALARIA CONTROL: THE PATIENTS' PERSPECTIVE

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The present study was undertaken to evaluate the cost-effectiveness of lambda-cyhalothrin-treated nets in comparison with conventional DDT-spraying as a method of malaria control according to the patients' perspective among migrant populations in a high-risk area along the Thai-Myanmar border in Thailand. Ten hamlets comprising 243 houses with 948 inhabitants were given only treated nets. Twelve hamlets comprising 294 houses and 1,315 inhabitants represented the DDT-treated area and another six hamlets with 171 houses and 695 inhabitants served as controls. Information as to consumer costs was obtained by interviewing 3,214 patients seeking care at all levels of the health care system in the study area. Analysis showed that the impregnated-net program was more cost-effective than the DDT-spraying program or surveillance

alone (US\$ 0.59 vs. US\$ 0.74 vs. US\$ 0.79 per 1 case of prevented malaria). We conclude that in a high-risk area such as along the Thai-Myanmar border in western Thailand, integrating the use of impregnated nets with large-scale primary health care programs is likely to constitute the most cost-effective method for controlling malaria according to the patients' perspective. ■

Published in: Southeast Asian J Trop Med Public Health 1999 Sept;30(3).

COST-EFFECTIVENESS ANALYSIS OF ARTESUNATE AND QUININE+TETRACYCLINE FOR THE TREATMENT OF UNCOMPLICATED FALCIPARUM MALARIA IN CHANTHABURI, THAILAND

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A randomized, controlled, malaria-clinic-based field trial was carried out to compare the cost-effectiveness of a 5-day 700-mg oral artesunate and a 7-day quinine+tetracycline regimen for the treatment of uncomplicated falciparum malaria in Thailand. Cost-effectiveness was determined from the providers' perspective and based on curative effectiveness. A total of 137 patients, aged 15-60 years, attending a malaria clinic were followed for 28 days, 60 of them received quinine+tetracycline and 77 received artesunate. Cure rates were assessed on day 5 (artesunate) and day 7 (quinine+tetracycline), using the intention-to-treat approach. Cost-effectiveness and sensitivity analysis were performed by varying the day 5/day 7 curative effectiveness and cost of artesunate. The cure rate with artesunate (100%) was more cost-effective than quinine+tetracycline (77.4%) (relative risk adjusted for sex (aRR) = 1.32, 95% confidence interval (CI) = 1.12-1.55; (referent quinine+tetracycline). Artesunate was more cost-effective than quinine+tetracycline at the following costs: artesunate ≤ US\$ 0.36 per 50-mg tablet; quinine US\$ 0.06 per 300-mg tablet; tetracycline US\$ 0.02

per 250-mg capsule; and services per case found ≤ US\$ 11.49. Because of the higher cure rate and higher cost-effectiveness of the artesunate regimen compared with quinine+tetracycline, we recommend its use for the treatment of uncomplicated falciparum malaria in malaria clinics in Thailand. ■

This study was supported by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

Published in: Bull WHO 1999;77(3):235-43.

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The Department of Tropical Hygiene is responsible for teaching, training and research in the field of epidemiology and hygiene. Most of the research activities related to tropical diseases are being conducted at the Suan Phung Research Unit in Ratchaburi Province. The Suan Phung Research Unit, supported by Her Royal Highness Princess Galayani Vadhana Krom Luang Naradhivas Rajanagarindra Fund, is one of the Faculty's research stations for conducting research on tropical diseases. Various activities at the Suan Phung Research Unit, such as the provision of health services for the local people and field epidemiology training for students, are conducted under the supervision of personnel from the Department of Tropical Hygiene.

Suan Phung is a small district in Ratchaburi Province located on the western border of Thailand with Myanmar. It has an area of 2,545 square kilometers, consisting of 7 sub-districts with 8,254 households and a population of 33,972. The population is mainly Thai-Karen, of low socio-economic status, who carry a Thai identity card. There is one community hospital with 50 beds and a total of 13 health centers. The common health problems of the people living in the area are: malaria, dengue hemorrhagic fever, filariasis, tropical skin diseases, intestinal helminthiasis, and malnutrition.

CURRENT RESEARCH ACTIVITIES

1. Epidemiology and control of malaria in Ratchaburi Province, Thailand.
2. Correlation between malaria incidence in Thailand and changes in vegetation cover using satellite remote sensing techniques.
3. Epidemiological study of nutritional deficiency among Karen preschool children.
4. Epidemiology and control of soil-transmitted helminthiasis in a rural community near the Thai-Burmese border.
5. Assessment of risk factors of mortality associated with vehicular crashes in a central province of Thailand: before and after enforcement of Safety Device Law, 1994-1998.



TEACHING AND TRAINING COURSES

The Department is responsible for the Faculty's teaching and training courses as well as international training courses in epidemiology.

1. Diploma in Tropical Medicine and Hygiene (D.T.M.&H.)

CORE SUBJECTS :

TMHG 501 : Tropical Hygiene

TMHG 502 : Medical Statistics

ELECTIVE SUBJECTS :

TMHG 508 : Epidemiology

TMHG 509 : Computer Utilization

2. M.Sc. and Ph.D. in Tropical Medicine

CORE SUBJECTS :

TMID 513 : Biostatistics

TMID 514 : Research Methodology and Design

ELECTIVE SUBJECTS :

TMHG 511 : Advanced Statistical Analysis in Biomedical Research

TMHG 512 : Modern Methods in Epidemiological Research

TMHG 513 : Use of Advanced Statistical Software in Epidemiological Analysis

TMHG 514 : Data Processing by Computer

TMHG 515 : Design and Analysis in Experimental Research

3. Master Degree in Primary Health Care Management

ADPM 606 : Epidemiological Studies in Health System

4. M.Sc. (Medical Epidemiology)

TMHG 668 : Epidemiological Methods

TMHG 676 : Epidemiology of Specific Health Problems

5. Ph.D. (Clinical Epidemiology)

RACE 606 : Advanced Epidemiological Methods



INTERNATIONAL LINKAGES

1. Research

- 1.1. Clinica di Malattie Infettive e Tropicali, Università Degli Studi Di Brescia.
- 1.2. Centre de Formation et de Recherche en Médecine et Santé Tropicales, Hôpital Felix Houphouët-Boigny, Marseille, France.
- 1.3. Department des Maladies Infectieuses et Tropicales, Hôpital de la Salpêtrière, Paris, France.
- 1.4. Association Santé Sud Medical Humanitarian French Association, Marseille, France.
- 1.5. Freie Universität Berlin.

2. International Training Courses

- 2.1 SEAMEO-TROPMED Network.
- 2.2 Tropical Health Program, University of Queensland Medical School, Australia.
- 2.3 College of Public Health, University of the Philippines, Manila, the Philippines.
- 2.4 Faculty of Public Health, University of Indonesia, Indonesia.
- 2.5 Institute for Medical Research, Malaysia.
- 2.6 Freie Universität Berlin, Germany.

SERVICES

I. Short Courses

Introductory Course in Epidemiology.
Advanced Course in Tropical Epidemiology (international). Computer Utilization.
Regional Workshop on Geographic Information System: Disease Mapping for Tropical Infections and Vector-Borne Diseases.

II. Medical Personnel Training Courses

Management in Malaria Control for Malaria Division Personnel (international).
Health Information System for Malaria Division Personnel (international).
Epidemiology of Malaria and Malaria Control for Medical Personnel (WHO nominees).

III. Other Services

Consultant in Research Methodology and Biostatistics Health Surveillance for the Expressways Personnel Malaria Field Research Station.



Abstracts

MALARIA IN TREE CROP PLANTATIONS IN SOUTH-EASTERN AND WESTERN PROVINCES OF THAILAND

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During the past three decades almost half of the existing natural tropical forests in Thailand have been destroyed and replaced by crops, rubber, coffee, fruit orchards (durian, rambutan, mangosteen) and other commercial plantations. In order to determine the proportion of malaria cases contracted from such commercial plantations, an epidemiological study was conducted between June 1996 to May 1997 in two districts, one in Pong Nam Ron, located in a south-eastern province near the Cambodian border and another in Sai-Yok, in a western province along the Myanmar border. Data were collected by passive case detection from patients attending the existing malaria clinics and active case detection by monthly malariometric survey in selected villages. All malaria cases were thoroughly investigated and classified according to exposure to different ecotypes prior to onset of malaria symptoms in the preceding two weeks. Malaria cases acquired from commercial plantations accounted for 35.2% and 11.2% in Pong Nam Ron and in Sai-Yok districts,

respectively. In such plantations, most of the malaria cases were contracted from fruit orchards and to a lesser extent from rubber and teak plantations. From this study it is evident that commercial plantations provide a significant site of malaria transmission in addition to the forest and foothill areas in Southeast Asia where efficient vectors such as *An. dirus* and *An. minimus* are prevalent and have adapted to such changed ecosystems. ■

Published in: Southeast Asian J Trop Med Public Health 1999;30(3) (in press).

EPIDEMIOLOGY OF FATAL VEHICULAR CRASHES IN SARABURI PROVINCE

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95% CI 1.2-11.6). Other factors related to fatal crashes were: crashes occurring at a blind curve (OR=1.8, 95% CI 1.04-3.1), crashes resulting from tire puncture (Fisher's exact test, $p < 0.05$), crashes resulting from overturned vehicle (OR=4.2, 95% CI 1.3-12.8), and crashes involving pedestrians (OR=3.7, 95% CI 1.7-7.8). However, multivariate analysis revealed that there were 3 factors that demonstrated a significant association with fatal outcome: drivers without license (OR=2.2, 95% CI 1.1-4.8), driving while intoxicated (OR=3.2, 95% CI 1.03-10.2), and crashes involving pedestrians (OR=2.4, 95% CI 1.2-13.2). ■

Submitted to: Southeast Asian J Trop Med Public Health.

The road traffic accident has become one of the most important killers in Thailand. The magnitude of the problem and the negligence in intervention made mortality from vehicular crashes rank second amongst the top ten leading causes of mortality in the country. This analytic cross-sectional study was conducted with the aim of determining the risk factors of fatal crashes and its magnitude of association. Saraburi Province was selected as the site of the study because the Saraburi-Muaklek highway was found to have the highest incidence of mortality from vehicular crashes. The study revealed that mortality from traffic accidents in Saraburi Province comprises 41% of the total number of vehicular crashes. Factors related to the drivers were found to have significant contributions to fatal outcome. These were: drivers without license (OR=2.8, 95% CI 1.4-5.4) and drivers who were less than or equal to 30 years old (OR=3.8,

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CURRENT RESEARCH ACTIVITIES

Research activities of the Department of Tropical Nutrition and Food Science are concerned with nutritional problems in Thailand such as micronutrient deficiencies, lifestyle and dietary patterns of different age groups, the impact of overnutrition, oxidative stress and antioxidants in relation to health, and the effect of smoking on work performance in relation to the phenotype of α_1 -antitrypsin. Furthermore, molecular biology in lung cancer, e.g. identification of gene mutation in Thai patients, is investigated. Food and health relationship in populations of Asian countries are of interest for study and the data will be compared.

At the present time using food practice as the way to disease prevention and treatment is particularly interesting. This is part of the project on development of food and medicinal plants.

The topics of the current research projects are as follows:

1. Food and health relationship in the Asian population.
2. Dietary pattern, lifestyle and nutritional status of health science university students in Bangkok.
3. Investigation of nutritional, health and dietary patterns of Thai elderly.
4. Serum leptin concentration in obese subjects.
5. Micronutrients and oxidative stress in obese subjects.
6. The effect of smoking on work performance in relation to the phenotype of α_1 -antitrypsin.
7. Identification of gene mutation in lung cancer cells in Thai patients.
8. Molecular biology of carcinogenesis in lung cancer.
9. Development of food and medicinal plants.



Abstracts

AFLATOXINS M₁ AND M₂ IN BREAST MILK

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Aflatoxin concentrations were investigated in breast milk of 124 lactating women whose age range was 16-42 years. Sixty-four mothers were from the Bangkok metropolitan area and 60 mothers were from Khon Kaen, northeast Thailand. The nutritional status assessed by anthropometric measurements, namely body mass index (BMI) and mid-upper arm circumference (MUAC), of the mothers in both groups were similar. The triceps skinfold thickness (TSK) and mid-upper arm muscle circumference (MUAMC) of mothers in Bangkok were significantly higher than those of mothers in Khon Kaen. Only aflatoxins M₁ and M₂ were found in the breast milk samples investigated. Aflatoxin M₁ (AFM₁) was detected in 10 (15.6%) and 14 (23.3%) breastmilk samples of mothers from Bangkok and Khon Kaen respectively. Aflatoxin M₁ was most frequently detected at a median concentration of 20 ng/l (range between 5 and 409 ng/l) for mothers from Bangkok, and

23 ng/l (range between 4 and 6,372 ng/l) for mothers from Khon Kaen. Aflatoxin M₂ was detected in 2 (3.1%) and 13 (21.7%) breastmilk samples for mothers from Bangkok and Khon Kaen respectively. The median concentration of aflatoxin M₂ (AFM₂) for milk samples of mothers from Bangkok was 10 ng/l (range between 5 and 15 ng/l), and 63 ng/l (range between 4 and 1,140 ng/l) for milk samples of mothers from Khon Kaen. Among these AFM₁ and AFM₂ contaminated milk samples, the mixture of AFM₁ and AFM₂ was shown in 1.6 and 13.3 per cent of breast milk samples from Bangkok and Khon Kaen respectively. These findings could be used to extrapolate that mothers from Khon Kaen had a higher risk of aflatoxin contaminated food consumption than mothers from Bangkok. It was found, from the data of 24-hour recall for dietary intake of mothers in Khon Kaen whose breastmilk was contaminated with aflatoxin, that the high risk food items for aflatoxin contamination were roasted ground chili, garlic, and glutinous rice contaminated with aflatoxin in the bamboo container. The risk food items for aflatoxin contamination consumed by mothers in Bangkok may be garlic, vegetable oil and drinking milk. ■

Published in: J Nutr Assoc Thailand 1999;33:42.



RELATIONSHIP BETWEEN SERUM C3 AND ANTINUCLEAR ANTIBODIES (ANA) IN 220 SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS IN INSTITUTE OF DERMATOLOGY, BANGKOK

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The relationship of serum complement (C3) level and antinuclear antibodies (ANA) titer in 220 follow-up cases (1-5 times) of systemic lupus erythematosus (SLE) at the Institute of Dermatology, Bangkok, were studied. There was a total of 307 serum samples studied. Patient ages ranged from 10-71 years. Sixteen percent (16%) were found to be negative, while 84% were positive for ANA. ANA patterns were speckled and speckled nucleolar in type. The range of serum complement (C3) level was 17-193 mg/dl (median=95 mg/dl, mean=93 mg/dl). There was a correlation between C3 level and ANA titer by Spearman's rank correlation ($r=-0.338$, $p<0.01$). ■

Submitted to: Bull Thai J Dermatol.

LEAD EXPOSURE, URINARY δ -AMINOLEVULINIC ACID CONCENTRATION AND HEMATOLOGICAL PARAMETERS OF ROAD SWEEPERS WORKING IN CONGESTED AREAS OF BANGKOK

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Road sweepers are especially exposed to environmental pollution. This study investigated the lead exposure, urinary δ -aminolevulinic acid concentration (ALA) and hematological parameters of road sweepers working in traffic congested areas of Bangkok. One hundred and ninety four apparently healthy road sweepers aged 20-59 years were investigated. One hundred and thirty nine staff from an academic institution served as controls. Both male and female road sweepers had slightly, but significantly, lower mean corpuscular hemoglobin concentration (MCHC) values. The white blood cell count (WBC) in female road sweepers was significantly higher compared with the female controls. The proportion of reticulocytes was higher in male and female road sweepers compared with the controls, while no difference was found in blood lead levels and ALA between male road sweepers and controls. Female road sweepers had slightly higher blood lead levels compared with the controls. ALA was not different between both groups of females. The proportion of road sweepers with basophilic stippling was more than double in comparison with the controls, contrary to expectations. Obvious signs and symptoms of lead poisoning were not evident in the group of road sweepers. There are, however, more discrete indications that working in this heavily polluted environment is not without health risks. ■

This work was partly supported by funds from the Department of Epidemiology, Institute of Social Medicine, Freie Universität Berlin, Germany.

Published in: J Nutr & Environ Med 1999;9:109-14.

LIPID PROFILES AND BLOOD PRESSURE IN RELATION TO BODY MASS INDEX (BMI) OF OVERWEIGHT AND OBESE THAI IN BANGKOK

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The lipid profiles, anthropometric measurements, including waist/hip ratio of 40 male and 166 female overweight (BMI ≥ 25.00 kg/m²) Thai volunteers who attended the Out-patient Department, General Practice Section, Rajvithi Hospital, Bangkok for physical check up during March-October 1998, were investigated. There was no significant difference between the median of age between sexes. The medians of height, weight and waist/hip ratio in males were significantly higher than those of female overweight and obese subjects. The prevalence of hypertension based on systolic and diastolic blood pressure of $\geq 160/95$ mmHg were 12.5% and 42.5% for males and 7.8% and 22.3% for females respectively. Overweight and obese males had significantly higher LDL-C, LDL-C/HDL-C ratios and TG, whereas HDL-C was lower when compared with females. Higher prevalence of LDL-C ≥ 150 mg/dl in males was found when compared with females. However, the opposite result was also observed for the prevalence of

low HDL-C (HDL-C ≤ 35 mg/dl), and 17.5% of total over-weight and obese subjects were found to be hypertriglyceridemic (TG ≥ 200 mg/dl).

In obese subjects (BMI ≥ 30.00 kg/m²), there were significant positive relationships between systolic, diastolic blood pressure, systolic blood pressure and serum HDL-C level as well as waist/hip ratio and serum LDL-C/HDL-C ratio or serum triglyceride whereas the opposite result was observed for waist/hip ratio and serum HDL-C. ■

Published in: Intern Med 1998;14:66-70.

URINARY IODINE EXCRETION AS A PREDICTOR OF THE IODINE CONTENT OF BREAST MILK

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Endemic goitre has re-emerged in Thailand. This is particularly dangerous for children, since iodine deficiency disorders (IDDs) might negatively influence their intellectual and mental development. In order to assess the situation, the iodine content of breast milk was determined and a method is proposed for monitoring IDD in lactating mothers further on. Eighty-five lactating women ranging from 15 to 45 years of age, from 12 villages of 3 districts, namely Chumpae, Srichompu and Pupaman within the mountainous areas of Khon Kaen Province, in the northeast of Thailand were investigated. The breast milk from 46.7 % of mothers was found to be below recommended standards. In addition, 52.0 % of women investigated had low urinary iodine excretion. The risk of women with low iodine excretion was 15-fold higher compared with women with sufficient iodine excretion to provide breast milk to their babies with insufficient iodine content. It is concluded that urinary iodine excretion can be used to monitor IDD in lactating mothers. ■

Partially supported by a research grant from the German Agency for Technical Co-operation.

Published in: J Med Assoc Thai 1999;82:284-9.

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CURRENT RESEARCH ACTIVITIES

1. Malaria: histopathologic and electronmicroscopic studies on various tissues and organs in humans.
2. Pathogenic effects of cytokines and nitric oxide in cerebral malaria.
3. Liver pathology in AIDS.
4. Evaluation of stool samples in HIV infected patients.
5. Opportunistic infections in AIDS.

AWARD

The research project on "Development of Oral Vaccine against Cholera" by Wanpen Chaicumpa, Manas Chongsa-nguan, Thareerat Kalambaheti, Yuwaporn Sakolvaree, Potjanee Srimanote, Pramuan Tapchaisri, Yuvadee Mahakunkijcharoen, Emsri Pongponrat*, Urai Chaisri*, Rujiporn Prateeprasen, Jiraporn Limpananont, Polrat Wilairatana, Sornchai Looareesuwan was awarded the **Best Research Work 1999** by the National Research Council of Thailand. Two researchers* from the Department of Tropical Pathology collaborated in part of the project.



Abstracts

ANTIPARASITE ADHERENCE ACTIVITY IN THAI INDIVIDUALS LIVING IN A *P. FALCIPARUM* ENDEMIC AREA

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Two types of antimalaria antibodies in the sera of 54 villagers living in a malaria endemic area of Thailand were determined by indirect immunofluorescence assay in order to define the status of malaria immunity within the group. Antibodies to parasite-derived antigens in the membrane of ring stage-infected erythrocytes were very high (1:1,250) in 44%, moderate to low (1:250) in 37% of the sera, and the rest did not have the antibody. However, all the sera had antibodies to antigens of the intraerythrocytic mature parasites, showing a very high level in 65%, and moderate to low levels in 37% of the sera. Sera with high antibody titers to either type of antigen significantly inhibited cytoadherence of *P. falciparum*-infected erythrocytes. All the sera variably inhibited rosette formation of the parasites but showed no association with the antibody titers. These results suggest that the antibodies to cytoadherence and rosette formation

can be elicited and sustained in the malaria-experienced host while living in the endemic area. This may be a natural preventive mechanism against the severity of *P. falciparum* infection in the infected host. How long the antiparasite adherence activity will last remains to be investigated. ■

Published in: Asian Pac J Allergy Immunol 1999;17:23-9.

INTRACEREBRAL HEMORRHAGE DUE TO NOSOCOMIAL ASPERGILLOSIS FOLLOWING NEUROSURGERY (CASE REPORT)

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A unique case of nosocomial aspergillosis following neurosurgery in a 10 year old girl was documented. She presented with intracerebral hemorrhage after three weeks of operation for evacuation of craniopharyngioma. To our knowledge, this is the first reported case of intracerebral hemorrhage due to nosocomial aspergillosis following neurosurgery. ■

Published in: Southeast Asian J Trop Med Public Health 1999;30(1):50-2.

A QUANTITATIVE ULTRASTRUCTURAL STUDY OF MALARIA PATHOLOGY IN THE BRAIN

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Brain tissues from 52 fatal cases of malaria were collected in Thailand and Vietnam. These were used for an electron microscopy study of the pathological features of cerebral and non-cerebral malaria in the brain. In particular, a quantitative analysis was made of the degree of parasitized red blood cells (PRBC) sequestration in cerebral microvessels in three different areas of the brain, the temporal cortex, cerebellum and medulla. Parasites were staged according to their expression of surface knob proteins and ultrastructural development. Other aspects of pathology were also counted, including the number of uninfected red cells, leukocytes, platelets and presence of fibrin thrombin within vessels. The

presence of extravascular leukocytes, PRBC and RBC was also counted.

Comparisons were made between different areas of the brain, between different individual cases and between groups of cerebral and non-cerebral malaria cases.

This study showed no evidence of differences in vascularity between patient groups, allowing direct comparison using a non-parametric Mann-Whitney U test. Significantly more PRBC sequestration was seen in the brains of cerebral malaria patients (CM) compared with non-cerebral cases (NCM) in the cerebral cortex and medulla ($p=0.04$ and $=0.02$ respectively). Within the CM group there was a marked trend for more knob + mature stages when sequestered parasites were seen ($p = 0.058$ and $= 0.025$ in cortex and medulla respectively). The same trends were noted in the cerebellum but were not statistically significant. More uninfected RBC were seen in CM cases, implying some degree of non-specific vascular congestion compared with NCM cases. Little evidence for marked accumulation of leukocytes or intravascular fibrin platelet thrombin was seen in either group.

Ultrastructural changes to endothelial cells were noted and will be demonstrated along with the composition of extravascular hemorrhages.

This study provides evidence for the quantitative association between PRBC sequestration in the brain and the clinical syndrome of cerebral malaria. ■

This study was supported by The Wellcome Trust of Great Britain and Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

Presented at: Joint International Tropical Medicine Meeting 1999, Bangkok, Thailand.

CYTOMEGALOVIRUS AND CRYPTOSPORIDIUM INFECTIONS IN AIDS: A NECROPSY STUDY (CASE REPORT)

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A case of coinfection of cytomegalovirus (CMV) and cryptosporidium in an AIDS patient is reported. Chronic diarrhea was the presenting symptom. Etiologic agents were diagnosed only at postmortem evaluation. CMV intranuclear inclusions were seen in the terminal ileum, colon and vermiform appendix. Cryptosporidium oocysts were also present in the intestinal brush border of the colon. Improvement of diagnostic procedures such as colonic biopsy and the use of appropriate staining procedure for AIDS patients with diarrhea can help identify the cause of illness. ■

Published in: Southeast Asian J Trop Med Public Health 1999;30(1):219-20.

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CURRENT RESEARCH ACTIVITIES

VACCINE

1. A phase IV, observed-blind, randomized, controlled trial to evaluate safety, tolerability and immunogenicity of the Chiron acellular pertussis vaccine combined with diphtheria and tetanus toxoids (DTaP), as compared to a licensed whole-cell pertussis vaccine combined with diphtheria and tetanus toxoids, (DTwP), when administered to healthy Thai infants at 2, 4 and 6 months of age.
2. Safety and immunogenicity of tetravalent dengue vaccine formulation in Thai adult volunteers.

MALARIA

1. Clinical efficacy and pharmacokinetics of suppositoried artesunate combined with mefloquine in the treatment of severe childhood falciparum malaria.
2. Clinical efficacy and pharmacokinetics of suppositoried artesunate combined with mefloquine in the treatment of uncomplicated childhood falciparum malaria.

DIARRHEA

1. A multicentric, randomized, double blind placebo-controlled, paralleled group study to assess the efficacy, safety and tolerability of acctorphan (Tiorfan™) 1.5 mg/kg/body weight tid po plus oral rehydration therapy in the treatment of acute diarrhea in children.

Abstracts

A NEW VERO CELL-RABIES VACCINE: RESULTS OF A COMPARATIVE TRIAL WITH HUMAN DIPLOID CELL RABIES VACCINE IN CHILDREN

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We evaluated the immunogenicity and safety of a chromatographically purified rabies vaccine (CPRV) compared with human diploid cell rabies vaccine (HDCV) after primary and booster pre-exposure immunizations. Intramuscular doses of either 0.5 mL CPRV or 1.0 mL HDCV were given to 400 schoolchildren on days 0, 7, 28 and 365 (booster). All children achieved adequate titers (≥ 0.15 IU/mL) 14 days following primary immunization with CPRV and HDCV, which persisted in all but one child up until one year. Fourteen days after primary immunization (day 42) and 7 days after booster (day 372), all children had titers ≥ 0.5 IU/mL. Local and systemic reactions after primary and booster immunizations occurred significantly less frequently in the CPRV group. A severe allergic reaction (angioedema) was reported in only one child after booster with HDCV. CPRV has adequate immunogenicity for primary and booster pre-exposure immunizations in children, and has a better safety profile than HDCV. ■

This study was supported by Pasteur Mérieux Connaught, Lyon, France.

Published in: CID 1999;29:141-9.



PERSISTENCE OF ANTIBODIES IN CHILDREN AFTER INTRADERMAL OR INTRAMUSCULAR ADMINISTRATION OF PRE-EXPOSURE PRIMARY AND BOOSTER IMMUNIZATIONS WITH PURIFIED VERO-CELL RABIES VACCINE

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Background: The use of intradermal (ID) injections of purified Vero-cell rabies vaccine (PVRV) for pre-exposure prophylaxis has not been well established. We studied the safety and immunogenicity of ID and intramuscular (IM) PVRV injections for primary and booster pre-exposure immunizations.

Methods: One of two rabies pre-exposure PVRV regimens comprising three doses of either 0.1 mL ID or 0.5 mL IM administered over 28 days was attributed at random to 190 school children. One booster dose was given a year later by either ID or IM route, according to their initial randomization group. Serologic results were available from 155 (82%) children at one year after primary immunization, and 118 (62%) children at two years after booster.

Results: Although children vaccinated ID had significantly lower rabies neutralizing antibody titers after primary immunization as well as after booster than children vaccinated IM ($P < 0.001$ for all time points), there were no significant differences in the percentages of children with CDC adequate titers (≥ 0.15 IU/mL) between the ID- and IM-groups following both primary- and booster-immunizations. Mild local reactions were more frequent after ID vaccination. Mild or moderate systemic reactions were infrequent and similar following ID and IM vaccinations. Fever and headache were reported by $\leq 6\%$. The reactions after booster were not different from those of post-primary immunization.

Conclusions: Purified Vero-cell rabies vaccine appears to be safe and immunogenic for primary and booster pre-exposure immunizations. An ID PVRV pre-exposure regimen should be useful especially for rabies-endemic countries with low per capita income. ■

This study was supported by Pasteur Mérieux Connaught, Lyon, France.

Published in: Pediatr Infect Dis J 1998;1001-7.

EVALUATION OF THE SAFETY, IMMUNOGENICITY, AND PHARMACOKINETIC PROFILE OF A NEW, HIGHLY PURIFIED, HEAT-TREATED EQUINE RABIES IMMUNOGLOBULIN, ADMINISTERED EITHER ALONE OR IN ASSOCIATION WITH A PURIFIED, VERO-CELL RABIES VACCINE

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A clinical evaluation of a new, purified, heat-treated equine rabies immunoglobulin 9 PHT-Erig, F9(ab') preparation, was carried out in Thailand and in the Philippines - two countries where rabies is endemic. An initial prospective, randomized, controlled trial (Study 1), compared the safety and pharmacokinetics (serum concentrations of rabies antibodies) after administration either of PHT-Erig or of a commercially-available equine rabies immune globulin (Erig PMC). A second trial (Study 2) simulated post-exposure rabies prophylaxis by using a reference cell culture vaccine, the purified Vero-cell rabies vaccine (PVRV0), administered in association with either Erig PMC or PHT-Erig. In Study 1, 27 healthy, Thai adults received a 40 IU kg⁻¹ dose of either Erig PMC ($n = 12$) or PHT-Erig ($n = 15$) via the intramuscular (IM) route; half of the dose was injected into the deltoid area and the other half into the buttocks. Serum for rabies antibody determination and F(ab')₂ concentration was collected at

hours (H) 0, 6 and 12, and on day (D) 2, 3, 4, 6, 8, 10, 12 and 15. Both products were safe, with no serious adverse events, and in particular, no anaphylactic reactions or serum sickness was reported. A statistical comparison of the pharmacokinetic parameters did not demonstrate bioequivalence of the two products. Nonetheless, the relative bioavailability of 93% and the similar absorption rates suggest the pharmacokinetic profiles of Erig PMC and PHT-Erig are similar. The antibody level in either group was low throughout the 15-day study period. The geometric mean titer (GMT) values ranged from group 0.027-0.117 IU ml⁻¹ in the Erig group and from 0.029 to 0.072 IU ml⁻¹ in the PHT-Erig. There was no significant difference between the evolution of GMT values for the two groups. In Study 2, 71 healthy volunteers received 40 IU ml⁻¹ via the intramuscular route of either Erig PMC ($n = 36$) or PHT-Erig ($n = 35$) on D0, in association with five doses of PVRV on D0, D3, D7, D14 and D28. No serious reactions were reported in either group. In particular, no immediate (anaphylactic type) or delayed (serum sickness) allergic reactions were observed. Over the 28-day follow-up period, GMT profiles of the two groups were statistically equivalent. On D14, 100% of the subjects had protective antibody titers (anti-rabies antibodies ≥ 0.5 IU ml⁻¹, which is the WHO-recommended level of seroconversion), and Erig PMC and PHT-Erig were indistinguishable according to the clinical definition chosen. On D28, the GMT values were 33.2 IU ml⁻¹ (95% CI, 23.8-46.1 IU ml⁻¹) in the Erig PMC/PVRV group and 31.4 IU ml⁻¹ (95% confidence interval, CI, 23.4-42.2 IU ml⁻¹) in the PHT-Erig/PVRV group, showing evidence of adequate vaccine-induced antibody responses in both groups. The increased purity, the heat-treatment step introduced in the manufacturing process of PHT-Erig, and the good clinical results substantiate the use of this new generation, purified equine F(ab')₂ preparation in the post-exposure prophylaxis of rabies. ■

This study was supported by Pasteur Mérieux Connaught, Lyon, France.

Published in: Acta Tropica 1998;70:317-33.

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CURRENT ACTIVITIES

The Department has had a number of significant achievements in three categories, as follows:

RESEARCH

There has been an extensive investigation of nutritional problems, such as the measurement of vitamin B₁₂ and folic acid levels, vitamin B₁₂ binding proteins or transcobalamin in serum and red blood cells of patients. Furthermore, erythrocyte glutathione peroxidase and serum selenium levels have been studied. The outstanding research works are :

1. Comparison of non-radiological technique and ¹²⁵I-labelled method for measurement of folic acid in human sera.
2. Serum vitamin B₁₂ determined by two radioassay methods.
3. Erythrocyte glutathione peroxidase (GSH-Px) and serum selenium levels in patients with cervical dysplasia.
4. The influence of vitamin B₁₂ and folate deficient indices on whole blood viscosity in pregnancy.
5. Study of transcobalamin II in serum of epilepsy patients.

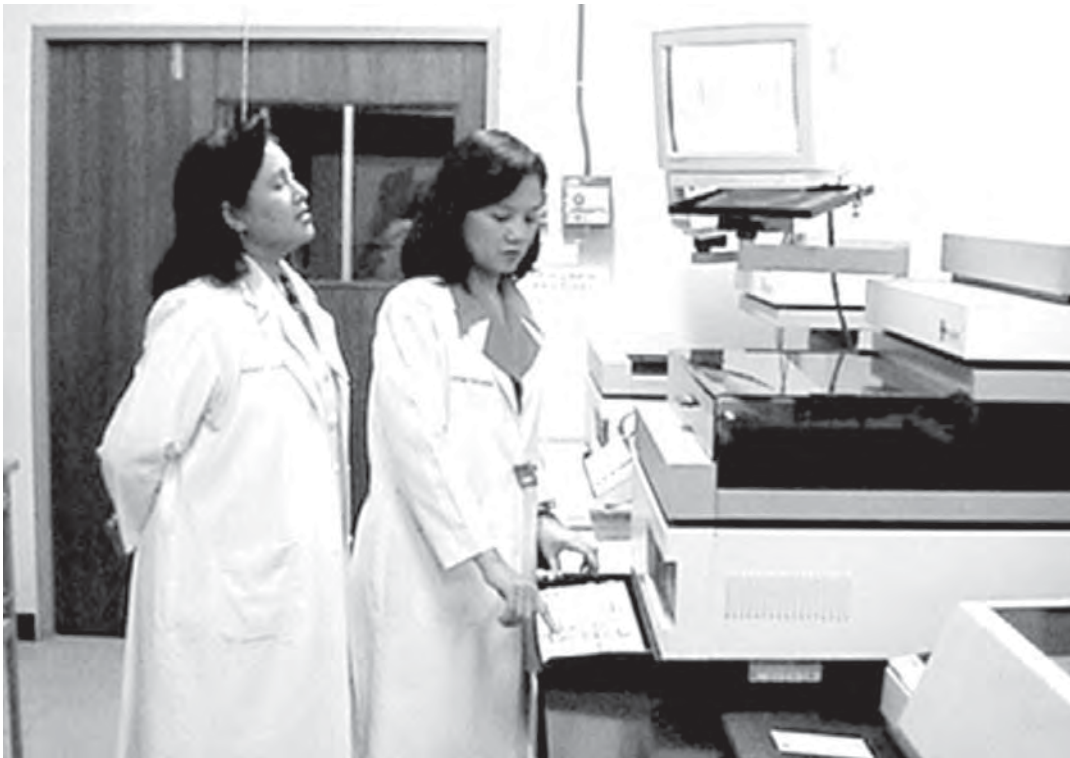


There is a number of other research works which are the result of interdepartmental cooperation, such as :

- Management of toxic substances and development of a database located in the Faculty of Tropical Medicine, Mahidol University.
- The correlation between folic acid status and cervical cytologic abnormality in Thai women.
- Lead exposure, urinary δ aminolevulinic acid concentrations and hematological parameters of road sweepers working in congested areas of Bangkok.
- Furthermore, Dr. Petcharindr Yamarat and Miss Cheeraratana Cheeramakara are working with a Japanese company conducting a clinical trial in HIV-infected patients in search of a drug to treat HIV, having the Head of the Department as a consultant.

TEACHING

The Department has provided facilities for assistance and service to two M.Sc. students (Faculty of Pharmacy) for their theses concerning folate deficiency in the epilepsy patient. In addition, assistance for one M.Sc. student (Faculty of Tropical Medicine) has been also provided as above. One Ph.D. student (Faculty of Tropical Medicine) has been enrolled in the Department since 1999.



The Department has provided two new subjects for the Ph.D. student, in addition to the teaching program of recent years. They are Radiation Protection (TMRD 505) and Radioisotopes in Medicine and Biology (TMRD 504). These subjects have been organized with the cooperation of the Department of Radiological Science, Faculty of Medicine, Ramathibodi Hospital and the Department of Tropical Nutrition and Food Science, Faculty of Tropical Medicine.

In addition, Miss Yupa Chantachum, one of the staff here, has been invited to be a lecturer in "Therapeutic drug monitoring" in the Faculty of Allied Health Sciences, Thammasart University. She remains head of the project under the Institute of Science and Technology for Research and Development, Mahidol University, for determination of heavy metals and trace elements using an atomic absorption spectrometer, which she has used for service as well. She is thesis advisor to M.Sc. students here and another student from Chulalongkorn University.

SERVICES

There are two projects established for services: (1) service for the measurement of folic acid in serum and in red blood cells; and (2) service for the measurement of vitamin B₁₂ in serum. The annual service details are shown below.

	Vitamin B ₁₂ number	Serum folate number	Red cell folate number
Child	-	4	2
Woman	211	255	96
Man	180	278	88
Total	391	537	186

It is calculated that the Department will return income as expense and profit to the Faculty of approximately 170,000.00 Baht.



Abstracts

FACTORS INFLUENCING BLOOD VISCOSITY: ADULT AND NEWBORN BLOOD ANALYSIS

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W Thanomsak**

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Our finding of a decrease in blood viscosity in newborn infants compared with adults led to analysis of this change by measuring blood viscosity, plasma fibrinogen concentration, plasma viscosity and mean corpuscular volume (MCV) of 24 adults and 16 newborn infants and investigating regression analysis between them.

Firstly, plasma proteins in newborn infants are synthesized less than in adults, therefore the plasma fibrinogen concentration in newborn infants is less than that of adults. This causes decreased blood viscosity in newborn infants compared with adults. Secondly, plasma viscosity of newborn infants is also less than that of adults. In the same way this causes a decrease in blood viscosity in the newborn. Thirdly, mean corpuscular volume (MCV) of newborn infants is more than that of adults because of young RBC. There is a negative correlation between blood viscosity and MCV. High MCV in newborn leads to low blood viscosity in newborns compared with adults. ■

Presented at: Joint International Tropical Medicine Meeting 1999 and The Fifth Chamlong-Tranakchit Harinasuta Lecture. 1999 Aug 4-6 Bangkok, Thailand.

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The Wellcome-Mahidol University Oxford Tropical Medicine Research Programme was initiated in 1979 to study the pathophysiological mechanisms, prevention and treatment of severe tropical infections including falciparum malaria, rabies and melioidosis.

The clinical work of the unit takes place in three up-country locations;

- in Mae Sot Provincial Hospital (studies of the pathophysiology and treatment of falciparum malaria),
- in the camps for displaced persons of the Karen ethnic minority on the north-western Thai-Myanmar border (studies of the epidemiology, prevention and treatment of malaria and tuberculosis),
- in Sappasitprasong Hospital Ubon Ratchatani (study of melioidosis and fungal infections in patients with AIDS).

The current malaria research activities of the unit include studies of pathophysiological mechanisms in severe malaria, descriptions of the pharmacokinetic and pharmacodynamic properties of antimalarial drugs, and studies of the epidemiology, prevention and treatment of malaria in the area of low or unstable transmission on the western border of Thailand.

This year we conducted studies of retinal capillary blood flow in severe malaria, comparative bioactivities of different artemisinin formulations, and mechanisms of parasite clearance. The Shoklo Malaria Research Unit conducted studies with artemether-lumefantrine and atovaquone-proguanil and large-scale studies of malaria in pregnancy and young children.

Studies of melioidosis include a large prospective clinical description of the disease, and a series of clinical and microbiological investigations to improve diagnosis and management of this important infection. This year, we completed studies of antimicrobial maintenance treatment, and began work on phagocytosis and killing.

Studies of fungal infections include a pharmacokinetic-pharmacodynamic evaluation of different treatment strategies in cryptococcal meningitis, and the development of improved methods to diagnose penicilliosis. This year we conducted studies on the pharmacokinetics and pharmacodynamics of different amphotericin B formulations.



Abstracts

NITRIC OXIDES IN PLASMA, URINE AND CEREBROSPINAL FLUID IN PATIENTS WITH SEVERE FALCIPARUM MALARIA

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It has been suggested that nitric oxide (NO) plays an important role in the pathogenesis of severe falciparum malaria. Since NO has a very short half-life, nitrate and nitrite (NO_x) levels, stable metabolites of NO, are used as measures of NO production. We measured plasma NO_x levels in 24 adults with severe falciparum malaria on the Thai-Burmese border. After correction for renal function, there was no correlation between plasma NO_x levels, or the total amount of NO_x excreted in the urine, and disease severity. Plasma NO_x levels decreased after the first 48 hr in all patients ($P=0.007$), suggesting decreased NO production. The NO_x levels in cerebrospinal fluid (CSF) correlated well with plasma NO_x levels, but these did not show a correlation with coma depth, and were not significantly different from those in a healthy control group. These findings do not support the hypothesis that excessive NO production contributes to the pathogenesis of severe falciparum malaria. However, local changes in NO production, e.g., in the central nervous system, might

not be reflected in the total NO_x production or NO_x levels in the CSF. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: Am J Trop Med Hyg 1998;59:497-502.

RED CELL DEFORMABILITY, SPLENIC FUNCTION AND ANEMIA IN THALASSEMIA

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Red cell deformability (RCD) was measured in 38 patients with β -thalassemia and 48 patients with β -thalassemia, of whom 13 had undergone splenectomy. All splenectomized patients, but none of those with intact spleens, had very rigid erythrocytes with an elongation index <0.45 at a high shear stress of 30 Pa suggesting a splenic recognition threshold for removal of rigid red cells. At this shear stress, RCD correlated strongly with the degree of anemia in both the splenectomized ($r=0.81$, $P<0.001$) and non-splenectomized (β -thalassemia patients (all patients $r=0.81$, $P<0.001$: homozygous β -thalassemic patients $r=0.51$, $P=0.01$). These data suggest that reduced RCD is a major determinant of anemia in thalassemia. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: Br J Haematol 1999;105:505-8.

QINGHAOSU IN COMBINATIONS

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Antimalarial combinations make therapeutic sense. As we have few antimalarial drugs and even fewer in development, and as the malaria parasite shows a remarkable ability to develop resistance, all possible measures should be taken to protect those drugs that we do have available. Although in experimental animals, combinations have been shown unequivocally to delay the onset of resistance, this has not yet been proved formally in human malaria. Yet formal proof is extremely difficult to obtain. However, there is sufficient circumstantial evidence to suggest that resistance can be delayed. As there are no counter arguments and the stakes are high, it seems reasonable that an artemisinin derivative should be combined with all slow acting antimalarial drugs. Those drugs with a particularly vulnerable profile, in which a single or double point mutation confers a high level of resistance, should not be deployed alone and should always be combined with an artemisinin derivative. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: Médecine Tropicale 1998;58:85-8.

ARTESUNATE VERSUS ARTEMETHER FOR THE TREATMENT OF RECRUDESCENT MULTIDRUG-RESISTANT FALCIPARUM MALARIA

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The therapeutic efficacy and toxicity of artesunate (2 mg/kg/day for five days, then 1 mg/kg/day for two days: total = 12 mg/kg) was compared with that of artemether (4 mg/kg followed by 2 mg/kg/day for two days, then 1 mg/kg/day for four days: total = 12 mg/kg) for the treatment of recrudescing multidrug-resistant falciparum malaria in an open randomized trial in 443 patients living on the western border of Thailand. Parasite and fever clearance times were similar in both groups; within 48 hr 94% (95% confidence interval [CI] = 91-96%) of the treated patients were a parasitemic and 93% (95% CI = 89-96%) were afebrile. Symptom resolution and resolution of hepatomegaly were slightly slower in the artesunate group; adjusted hazards ratio = 1.5 (95% CI = 1-2.0, P<0.01) and 2.2 (95% CI = 1.4-8, P=0.04), respectively. There was no significant difference in times to resolution or development of anemia or splenomegaly between treatment groups. By day 28, 3% (95% CI = 0.3-5%) of the patients treated with artesunate and 6% of those treated with artemether (95% CI = 2-9%) had recurrent infections (P=0.3). Both regimens were very well tolerated, with no significant adverse effects attributable to either derivative. Overall, these data suggest that the two oral artemisinin derivatives are safe, highly effective, and result in equivalent therapeutic responses in the treatment of drug-resistant falciparum malaria. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: Am J Trop Med Hyg 1998;59:883-8.

APPLICATION OF GENETIC MARKERS TO THE IDENTIFICATION OF RECRUDESCENT *PLASMODIUM FALCIPARUM* INFECTIONS ON THE NORTHWESTERN BORDER OF THAILAND

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Parasite genotyping by polymerase chain reaction was used to distinguish recrudescence from newly acquired *Plasmodium falciparum* infections in a Karen population resident on the northwestern border of Thailand, where malaria transmission is low (one infection/person/year). *P. falciparum* infections were genotyped for allelic variation in three polymorphic antigen loci, merozoite surface proteins-1 and -2 (MSP-1 and -2) and glutamate-rich protein (GLURP), before and after antimalarial drug treatment. Population genotype frequencies were measured to provide the baseline information to calculate the probability of a new infection with a different, or the same, genotype to the initial pretreatment isolate. Overall, 38% of the infections detected following treatment had an identical genotype

before, and up to 121 days after, treatment. These post-treatment genotypes were considered recrudescence because of the low (<5%) probability of repeated occurrence by chance in the same patient. This approach allows studies of antimalarial drug treatment to be conducted in areas of low transmission, since recrudescences can be distinguished confidently from newly acquired infections. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: Am J Trop Med Hyg 1999;60:14-21.

A COMPARISON OF LYSIS CENTRIFUGATION, POUR PLATE, AND CONVENTIONAL BLOOD CULTURE METHODS IN THE DIAGNOSIS OF SEPTICEMIC MELIOIDOSIS

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Aims - To determine whether quantitative blood culture methods could improve the diagnosis of septicemic melioidosis.

Methods - A comparison of conventional broth based blood cultures, a pour plate method, and a commercial lysis centrifugation (Isolator 10™ blood culture system) was conducted in 71 Thai patients with severe melioidosis. The time to identification of *B. pseudomallei* was recorded for each method.

Results - 42 patients (59%) were septicemic. Compared with conventional blood culture, the Isolator and pour plate methods had sensitivities of 81% and 61%, respectively. The median times to a positive culture were: Isolator 39.3 hours, pour plate 45.5 hours, broth culture 61.8 hours ($P < 0.001$ Isolator vs broth). There was a significant inverse correlation between Isolator tube or pour plate quantitative counts and time to detection ($g = -0.44$ and -0.57 , respectively). Mortality was higher in patients who were septicemic.

Conclusions - Routine use of one of these quantitative methods, in addition to conventional broth culture, may lead to earlier diagnosis of septicemic melioidosis. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: J Clin Pathol 1999;52:616-9.

COMPARISON OF IMIPENEM AND CEFTAZIDIME AS THERAPY FOR SEVERE MELIOIDOSIS

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An open, prospective, randomized, comparative treatment trial was conducted to compare the therapeutic efficacy of high-dose intravenous imipenem and ceftazidime for acute severe melioidosis. Adult Thai patients with suspected acute, severe melioidosis were randomized to receive either imipenem, at a dosage of 50 mg/(kg d), or ceftazidime, at a dosage of 120 mg/(kg d), for a minimum of 10 days. The main outcome measures were death or treatment failure. Of the 296 patients enrolled, 214 had culture-confirmed melioidosis, and 132 (61.7%) of them had positive blood cultures. Mortality among patients with melioidosis was 36.9% overall. There were no differences in survival overall ($P=0.96$) or after 48 hours ($P=0.3$). Treatment failure after 48 hours was more common among patients treated with ceftazidime ($P=0.011$). Both treatments were well tolerated. Imipenem

is a safe and effective treatment for acute severe melioidosis and may be considered an alternative to ceftazidime. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: Clin Infect Dis 1999;29:381-7.

ASSESSMENT OF THE NEUROTOXICITY OF PARENTERAL ARTEMISININ DERIVATIVES IN MICE

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In all experimental mammals tested (rats, dogs, primates), intramuscular injections of the oil-soluble antimalarial artemisinin derivatives artemether and artesunate have produced an unusual pattern of selective damage to brain stem centers predominantly involved in auditory processing and vestibular reflexes. Artesunate, the most widely used of these compounds, is a water soluble hemisuccinate derivative given parenterally either by intravenous or intramuscular injection. The neurotoxic potential of parenteral artesunate and artemether was compared in a murine model. Adult Swiss albino mice were assigned randomly to 28-day regimens of intramuscular artemether or artesunate in doses ranging from 30 to 100 mg/kg/day. At 30 mg/kg/day, no abnormalities were detected with either drug. At 50 mg/

kg/day, abnormalities were observed in six of 12 artemether recipients and two of 12 artesunate recipients. These were reversible in all but one (artemether) mouse. At 100 mg/kg/day, eight of 36 artemether recipients, two of 36 artesunate recipients, and one of 18 control mice died. All but four surviving mice in the artemether group (86%) showed obvious and usually irreversible abnormalities of balance and equilibrium, whereas only four artesunate recipients (11%) exhibited abnormalities, and these were reversible in each case ($P<0.001$). At this dose the relative risk (95% confidence interval) for death or disability was 5.3 (2.6-11.2) for artemether recipients. Intramuscular artemether is significantly more neurotoxic than intramuscular artesunate in this murine model. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: Am J Trop Med Hyg 1998;59:519-22.

TREATMENT OF VIVAX MALARIA ON THE WESTERN BORDER OF THAILAND

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The efficacy of chloroquine (25 mg base/kg over 3 days) in *Plasmodium vivax* malaria was evaluated in 1995/96 in 342 patients living in an endemic area on the western border of Thailand. Clearance of fever and parasites was obtained within 2 days in >95% of the patients, and all were aparasitemic by day 4. Reappearance of *P. vivax* occurred in 1 patient on day 21 and in 8 by day 28, giving a 28-day cure rate of 97% [95% confidence interval (CI) 95-99%]. By day 63, the relapse/re-infection rate was 63% (95% CI 57-69%). Most reappearances of parasitemia (85%; 121/143) were symptomatic. These patients were retreated either with chloroquine alone ($n=70$) or with chloroquine and primaquine (0.25 mg/kg daily for 14 days) ($n=43$). Only 1 patient (in the chloroquine-only group) had prolonged parasite clearance (D8) and he developed recurrent *P. vivax* by day 21, suggesting possible

recrudescence. The addition of primaquine to chloroquine reduced the risk of having a third vivax episode within 2 months by 96% (95% CI 83-99%). This resulted in a significantly higher hematocrit at day 42 despite a greater decrease in hematocrit during the first week of treatment with chloroquine-primaquine ($P=0.04$). Chloroquine remains highly effective on the western border of Thailand and the use of strictly supervised primaquine effectively prevents relapse. The introduction of primaquine on a large scale in an endemic area still requires a long-term risk-benefit assessment which must take into account potential toxicity, low compliance and reductions in the incidence and severity of *P. falciparum* infections by co-existent *P. vivax*. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: *Trans R Soc Trop Med Hyg* 1999;93:433-8.

NEUROPSYCHIATRIC ADVERSE EFFECTS OF MEFLOQUINE (WHAT DO WE KNOW AND WHAT SHOULD WE DO?)

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Malaria is still one of the most important tropical diseases, killing millions every year. The number of effective drugs is limited, because of the ability of the causative parasite *Plasmodium falciparum* to develop drug resistance. Mefloquine, if possible in combination with an artemisinin derivative, is the only efficacious treatment left for uncomplicated but highly multidrug-resistant *P. falciparum* infections encountered in some areas. Mefloquine remains effective in most endemic areas worldwide for both prophylaxis and treatment of malaria.

Generally, mefloquine is well tolerated but it is associated occasionally with neuropsychiatric adverse effects,

whether used as treatment or for prophylaxis. In recent years, mefloquine has acquired a bad reputation mainly because of reports of neuropsychiatric reactions in travellers. These reports were widely publicized and amplified by the media. As a result, the confusion about recommendations for the prophylaxis of malaria has deepened, and decisions on prophylactic regimens have been made that could have serious consequences. However, there is little evidence that the use of mefloquine should be avoided because of the risk of these adverse effects. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: *CNS Drugs* 1999;11:1-8.

THE EFFECTS OF MEFLOQUINE TREATMENT IN PREGNANCY

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We investigated the relationship between mefloquine antimalarial treatment and the outcome of pregnancy in Karen women living in an area along the western border of Thailand where multidrug-resistant *Plasmodium falciparum* infections are common. Of 3,587 pregnancies investigated, 208 (5.8%) were exposed to mefloquine, 656 (18.3%) to quinine only, and 909 (25.3%) to other antimalarials, and 2,470 (68.9%) had no documented malaria. There were 61 stillbirths and 313 abortions. Women who received mefloquine treatment during, but not before, pregnancy had a significantly greater risk of stillbirth than did women treated with quinine alone (odds ratio [OR], 4.72; 95% confidence interval [CI], 1.7-12.7), women exposed to other treatments (OR, 5.10; 95% CI, 2-13.1), and women who had no malaria (OR, 3.50; 95% CI, 1.6-7.6) ($P < 0.01$). This association remained after

adjustment for all identified confounding factors. Mefloquine was not associated with abortion, low birth weight, neurological retardation, or congenital malformations. Mefloquine treatment during pregnancy was associated with an increased risk of stillbirth. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: *Clin Infect Dis* 1999;28:808-15.

RED CELL SELECTIVITY IN MALARIA: A STUDY OF MULTIPLE-INFECTED ERYTHROCYTES

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To characterize red cell susceptibility to invasion in malaria, a selectivity index (SI) was calculated as the ratio of the observed number of multiple-infected red cell to that expected from a random process (Poisson distribution). In patients with falciparum malaria ($n=100$) SI decreased with increasing parasitemia ($P < 0.001$), and correlated inversely with plasma lactate concentrations, chosen prospectively as a measure of disease severity ($r = -0.36$, $P < 0.001$). For parasitemias $< 5\%$, the SI was lower in patients with severe malaria (geometric mean 1.35; 95%

confidence interval 1.01-1.80) than in uncomplicated malaria (2.31; 1.89-2.81; $P = 0.003$), despite similar parasite counts. The geometric mean (range) SI in vivax malaria ($n=20$), 7.69 (1.67, 29.75), was significantly greater than that in falciparum malaria at comparable parasitemias ($\leq 2\%$), 2.44 (0.45, 14.05), $P < 0.001$, suggesting that about 13% of circulating erythrocytes were susceptible to invasion by *Plasmodium vivax*. This translates into susceptibility for about 2 weeks after emergence from the bone marrow, if age is the sole determinant of this process. In falciparum malaria, selectivity was inversely proportional to severity; lack of selectivity could reflect either a "favourable" host red cell phenotype, or an indiscriminate parasite population. Both are dangerous for the host. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: *Trans R Soc Trop Med Hyg* 1999;93:165-8.

A QUANTITATIVE ANALYSIS OF THE MICROVASCULAR SEQUESTRATION OF MALARIA PARASITES IN THE HUMAN BRAIN

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Microvascular sequestration was assessed in the brains of 50 Thai and Vietnamese patients who died from severe malaria (*Plasmodium falciparum*, 49; *P. vivax*, 1). Malaria parasites were sequestered in 46 cases; in 3 intravascular malaria pigments but no parasites were evident; and in the *P. vivax* case there was no sequestration. Cerebrovascular endothelial expression of the putative cytoadherence receptors ICAM-1, E-selectin, and chondroitin sulfate and also HLA class II was increased. The median (range) ratio of cerebral to peripheral blood parasitemia was 40 (1.8 to 1,500). Within the same brain, different vessels had discrete but different populations of parasites, indicating that the adhesion characteristics of cerebrovascular endothelium change asynchronously during malaria and also that significant recirculation of parasitized erythrocytes following sequestration is unlikely. The median (range) ratio of schizonts to trophozoites (0.15:1; 0.0 to 11.7) was significantly lower than predicted from the parasite life cycle ($P < 0.001$). Antimalarial treatment arrests development at the trophozoite stages, which remain sequestered in the brain. There were significantly more ring form parasites (age <26 hours) in the cerebral microvasculature (median range: 19%; 0-90%) than expected from free mixing of these cells in the systemic circulation (median range ring parasitemia: 1.8%; 0-36.2%). All developmental stages of *P. falciparum* are sequestered in the brain in severe malaria. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: *Am J Pathol* 1999;155:395-410.

EFFICACY OF SIX DOSES OF ARTEMETHER-LUMEFANTRINE (BENFLUMETOL) IN MULTIDRUG-RESISTANT *PLASMODIUM FALCIPARUM* MALARIA

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The new oral fixed combination artemether-lumefantrine (CGP 56697) has proved to be an effective and well-tolerated treatment of multi-drug resistant *Plasmodium falciparum* malaria, although cure rates using the four-dose regimen have been lower than with the currently recommended alternative of artesunate-mefloquine. Two six-dose schedules (total adult dose = 480 mg of artemether and 2,880 mg of lumefantrine) were therefore compared with the previously used four-dose regimen (320 mg of artemether and 1,920 mg of lumefantrine) in a double-blind trial involving 359 patients with uncomplicated multidrug-resistant falciparum malaria. There were no differences between the three treatment groups in parasite and fever clearance times, and reported adverse effects. The two six-dose regimens gave adjusted 28-day cure rates of 96.9% and 99.12%, respectively, compared with 83.3% for the four-dose regimen ($P < 0.001$). These six-dose regimens of artemether-lumefantrine provide a highly effective and very well-tolerated treatment for multidrug-resistant falciparum malaria. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: *Am J Trop Med Hyg* 1999;60:936-42.

CLINICAL PHARMACOKINETICS AND PHARMACODYNAMICS OF ARTEMETHER-LUMEFANTRINE

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The combination of artemether and lumefantrine (benflumetol) is a new and very well tolerated oral antimalarial drug, effective even against multidrug-resistant falciparum malaria. The artemether component is absorbed rapidly and biotransformed to dihydroartemisinin, and both are eliminated with terminal half-lives of around 1 hour. These are very active antimalarials which give a rapid reduction in parasite biomass and consequent rapid resolution of symptoms. The lumefantrine component is absorbed variably in malaria, and is eliminated more slowly (half-life of 3 to 6 days). Absorption is very dependent on coadministration with fat, and so improves markedly with recovery from malaria.

Thus artemether clears most of the infection, and the

lumefantrine concentrations that remain at the end of the 3- to 5-day treatment course are responsible for eliminating the residual 100 to 10,000 parasites. The area under the curve of plasma lumefantrine concentrations versus time, or its correlate the plasma concentration on day 7, has proved an important determinant of therapeutic response. Characterization of these pharmacokinetic-pharmacodynamic relationships provided the basis for dosage optimization, an approach that could be applied to other antimalarial drugs. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: Clin Pharmacokinet 1999;37:105-25.

ANTIMALARIAL DRUG RESISTANCE AND COMBINATION CHEMOTHERAPY

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Antimalarial drug resistance develops when spontaneously occurring parasite mutants with reduced susceptibility are selected, and are then transmitted. Drugs for which a single point mutation confers a marked reduction in susceptibility are particularly vulnerable. Low clearance and a shallow concentration-effect relationship increase the chance of selection. Use of combinations of antimalarials that do not share the same resistance mechanisms will reduce the chance of selection because the chance of resistant mutant surviving is the

product of the per parasite mutation rates for the individual drugs, multiplied by the number of parasites in an infection that are exposed to the drugs. Artemisinin derivatives are particularly effective combination partners because (i) they are very active antimalarials, producing up to 10,000-fold reductions in parasite biomass per asexual cycle; (ii) they reduce malaria transmissibility; and (iii) no resistance to these drugs has been reported yet. There are good arguments for no longer using antimalarial drugs alone in treatment, and instead always using a combination with artemisinin or one of its derivatives. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: Philos Trans R Soc Lond 1999;354:739-49.

MALARIA: NEW DEVELOPMENTS IN TREATMENT AND PREVENTION

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Malaria still kills some 0.5-2.5 million people per year in the tropics. Resistance to the cheap, most commonly used antimalarials continues to spread alarmingly and could outpace drug development. The artemisinin derivatives have had an important clinical impact both on the treatment of resistant falciparum malaria and on the incidence of disease in low-transmission areas. A few promising new antimalarials are being tested clinically but there is an imperative need for cheap, well-tolerated drugs that can be used in short courses, and for strategies to delay the onset of drug resistance. Bed nets have been shown to reduce the incidence of severe malaria in many areas but an effective vaccine is urgently needed. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: Ann Rev Med 1999;50:179-92.

PHARMACOKINETICS OF QUININE AND 3-HYDROXYQUININE IN SEVERE FALCIPARUM MALARIA WITH ACUTE RENAL FAILURE

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The plasma concentrations of quinine and its main metabolite, 3-hydroxyquinine (3OHQn), were measured in 5 adult Thai patients with severe *Plasmodium falciparum* malaria and acute renal failure. Two patients required peritoneal dialysis but all survived. During acute renal failure, plasma concentrations of 3OHQn rose to reach up to 45% of the levels of the parent compound. The estimated median (range) quinine clearance was 0.83 mL/kg/min (0.58-1.16), and 3OHQn clearance/fraction of quinine converted was 3.40 mL/kg/min (2.58-4.47). The estimated 3OHQn terminal elimination half-life was 21 h (16.5-32.5). These data suggest that 3OHQn contributes about 12% of the antimalarial activity of the parent compound in patients with falciparum malaria and acute renal failure. It is also

likely that 3OHQn contributes to adverse effects, although this metabolite is not quantitated routinely by current high-performance liquid chromatography quinine assays. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: Trans R Soc Trop Med Hyg 1999;93:69-72.

ADVERSE EFFECTS IN PATIENTS WITH ACUTE FALCIPARUM MALARIA TREATED WITH ARTEMISININ DERIVATIVES

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In prospective studies of acute uncomplicated, multidrug-resistant falciparum malaria on the western border of Thailand, the oral artemisinin derivatives were used alone in the treatment of 836 patients (artesunate 630, artemether 206), were combined with mefloquine (15-25 mg base/kg) in 2,826 patients, and mefloquine alone was used in 1,303 patients. The combined regimens of mefloquine plus an artemisinin derivative were associated with more side effects than those with an artemisinin derivative alone; acute nausea (31% versus 16%), vomiting (24% versus 11%), anorexia (51% versus 34%), and dizziness (47% versus 15%) ($P < 0.001$). Oral artesunate and artemether alone were very well tolerated. There was no difference in the incidence of possible adverse effects between the two drugs, and no evidence that either derivative caused allergic reactions, neurologic or psychiatric reactions, cardiovascular or dermatologic toxicity. Blackwater fever occurred in three

patients treated with mefloquine plus artesunate regimens. Oral artesunate and artemether are safe and well tolerated antimalarial drugs. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: *Am J Trop Med Hyg* 1999;60:547-55.

RISK FACTORS FOR GAMETOCYTE CARRIAGE IN UNCOMPLICATED FALCIPARUM MALARIA

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The factors affecting the development of patent *Plasmodium falciparum* gametocytemia were assessed in 5,682 patients entered prospectively into a series of antimalarial drug trials conducted in an area of low and seasonal transmission on the western border of Thailand. Of the 4,565 patients with admission thick smear assessments, 110 (2.4%) had gametocytemia. During the follow-up period 170 (3%) of all patients developed patent gametocytemia, which in 89% had developed by day 14 following treatment. In a multiple logistic regression model, five factors were found to be independent risk factors at presentation for the development of persistence of gametocytemia during following up; patent gametocytemia on admission (adjusted odds ratio [AOR] = 7.8, 95% confidence interval [CI] = 3.7-16, $P < 0.001$), anemia (hematocrit $< 30\%$) (AOR = 3.9, 95% CI = 2.3-6.5, $P < 0.001$), no coincident *P. vivax* malaria (AOR = 3.5, 95% CI = 1.04-11.5, $P < 0.04$), presentation with a recrudescence infection

(AOR = 2.3, 95% CI = 1.3-4.1, $P < 0.004$), and a history of illness longer than two days (AOR = 3.3, 95% CI = 1.7-6.6, $P < 0.001$). Patients whose infections responded slowly to treatment or recrudescence subsequently were also more likely to carry gametocytes than those who responded rapidly or were cured (relative risks = 1.9, 95% CI = 1.3-2.7 and 2.8, 95% CI = 2.0-4.0, respectively; $P < 0.001$). These data provide further evidence of important epidemiologic interactions between *P. falciparum* and *P. vivax*, and drug resistance and transmission potential. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: *Am J Trop Med Hyg* 1999;60:1019-23.

PHARMACOKINETICS OF MEFLOQUINE COMBINED WITH ARTESUNATE IN CHILDREN WITH ACUTE FALCIPARUM MALARIA

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2 without food. Delaying administration of mefloquine until day 2 was associated with a mean (95% confidence interval) increase in estimated oral bioavailability of 72% (36 to 109%). On day 2, coadministration with food did not increase mefloquine absorption significantly, and there were no significant differences between patients receiving split- and single-dose administration. In combination with artesunate, mefloquine administration should be delayed until the second or third day after presentation. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: Antimicrob Agents Chemother 1999;43:341-6.

DIAGNOSIS OF *PENICILLIUM MARNEFFEI* INFECTION BY QUANTITATION OF URINARY ANTIGEN BY USING AN ENZYME IMMUNOASSAY

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reactive. At a cutoff titer of 1:40, the urine antigen detection assay had a diagnostic sensitivity of 97% and specificity of 98% (positive predictive value, 84%; negative predictive value, 99.7%). This test offers a valuable and rapid method for the diagnosis of penicilliosis in patients with AIDS and could be a useful addition to conventional diagnosis methods in areas in which penicilliosis is endemic. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: J Clin Microbiol 1999;37:117-21.

Combining artemisinin or a derivative with mefloquine increases cure rates in falciparum malaria patients, reduces transmission, and may slow the development of resistance. The combination of artesunate, given for 3 days, and mefloquine is now the treatment of choice for uncomplicated multidrug-resistant falciparum malaria acquired on the western or eastern borders of Thailand. To optimize mefloquine administration in this combination, a prospective study of mefloquine pharmacokinetics was conducted with 120 children (4 to 15 years old) with acute uncomplicated falciparum malaria, who were divided into four age- and sex-matched groups. The patients all received artesunate 4 mg/kg of body weight/day orally for 3 days and mefloquine as either (i) a single dose (25 mg/kg) on day 2 with food, (ii) a split dose (15 mg/kg on day 2 and 10 mg/kg on day 3) with food, (iii) a single dose (25 mg/kg) on day 0 without food, or (iv) a single dose (25 mg/kg) on day

P*enicillium marneffe* is a major cause of opportunistic infection in patients with AIDS in north and northeastern Thailand. A method for the quantitation of *P. marneffe* antigen in urine was developed by using fluorescein isothiocyanate-labelled purified rabbit hyperimmune immunoglobulin G in an enzyme-linked immunosorbent assay. This method was evaluated with 33 patients with culture-proven penicilliosis and 300 controls (52 healthy subjects, 248 hospitalized patients without penicilliosis) from the same area in which penicilliosis is endemic. Urinary antigen was found in all 33 (100%) patients with penicilliosis, with a median titer of 1:20,480. With undiluted samples, 67 (27%) of 248 hospital patients and 3 (6%) of 52 healthy controls were



A COMPARISON OF CHLORAMPHENICOL, TRIMETHOPRIM-SULFAMETHOXAZOLE, AND DOXYCYCLINE WITH DOXYCYCLINE ALONE AS MAINTENANCE THERAPY FOR MELIOIDOSIS

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A prospective, open, randomized, comparative treatment trial was conducted to compare the therapeutic efficacy of the conventional four-drug combination (chloramphenicol, trimethoprim-sulfamethoxazole, and doxycycline) with that of doxycycline alone in oral maintenance treatment of melioidosis. Adult Thai patients with culture-confirmed melioidosis were randomized to receive treatment with either regimen for a minimum of 12 weeks, usually following intravenous treatment of severe disease. The main outcome measure was culture-confirmed relapse. One hundred and sixteen patients were enrolled; 109 had culture-confirmed melioidosis, and 87 were considered

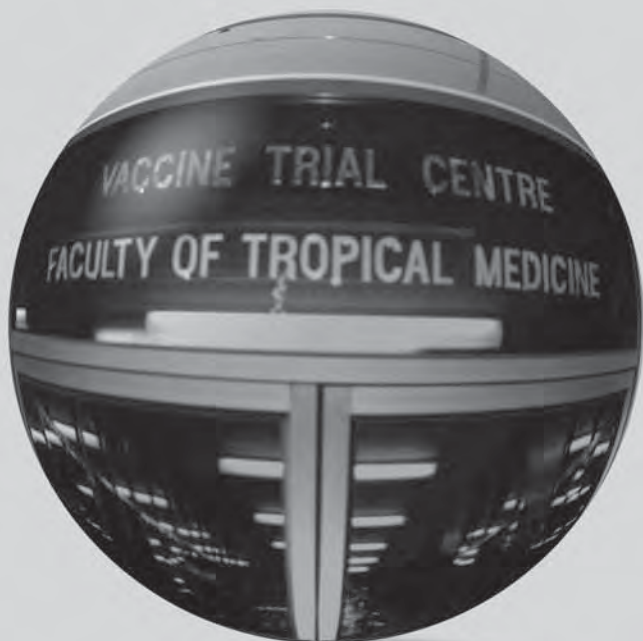
evaluable (43 had received doxycycline). Culture-confirmed relapse occurred in one patient randomized to the conventional regimen and in 11 (25.6%) randomized to the doxycycline regimen ($P=0.009$), and treatment failed for 8 (18.2%) versus 20 (46.5%), respectively ($P=0.009$). Adverse effects occurred in 26% of patients overall. Doxycycline alone cannot be recommended for a first-line regimen of oral maintenance treatment of melioidosis. ■

Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.

Published in: Clin Infect Dis 1999;29:375-80.

VACCINE TRIAL CENTRE

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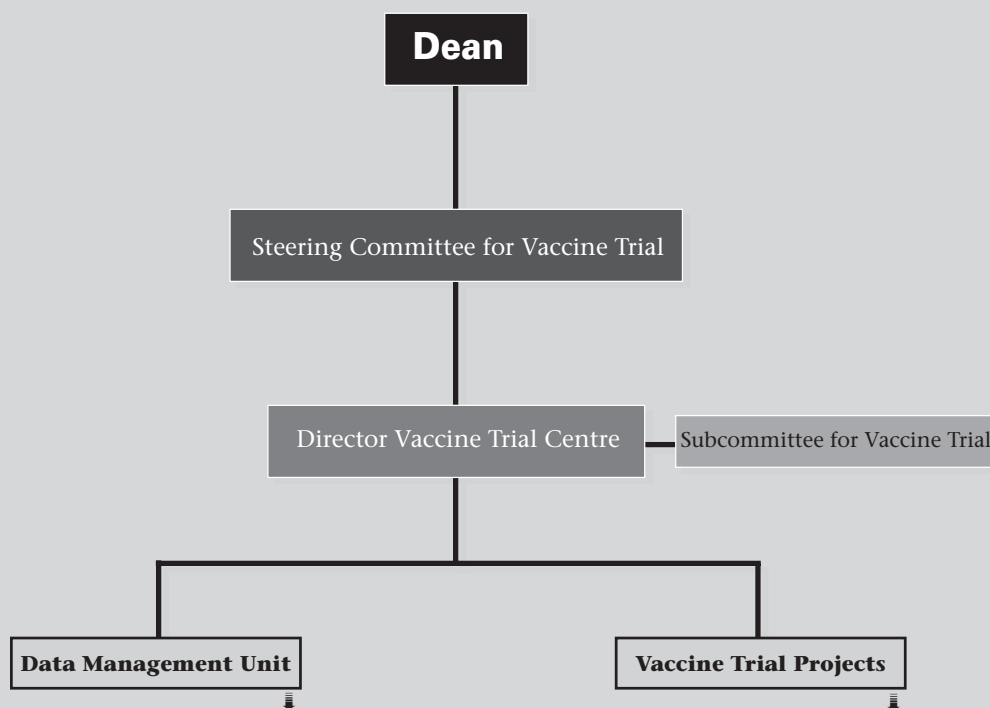


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Organization Chart



VACCINE TRIAL CENTRE

The development of vaccines against a number of infectious agents is reaching the point where evaluation of reactogenicity, immunogenicity, and protective efficacy must be evaluated in humans. These critical steps in vaccine development are best done initially in a controlled clinical facility where maximum information can be obtained from each study and where risks to study subjects or to the public can be prevented or limited.

BACKGROUND & RATIONALE OF ESTABLISHMENT

In spite of advancement in medical technology and therapeutics, infectious diseases including diarrheal diseases still cause health problems with high morbidity and mortality, particularly in developing tropical countries. To achieve effective control of the diseases, new and better tools for prevention, including vaccines are needed. Vaccine development and implementation has been considered of vital importance.

Recognizing the urgent need of another controlled clinical facility for evaluation of reactogenicity and protective efficacy of newly developed vaccines against infectious agents in human, the World Health Organization Special Programme on Control of Diarrhoeal Diseases supported the establishment of such a facility in the tropics, where diarrheal diseases are endemic and the vaccines specifically needed are different from Western countries. With the initiation of Professor Dr. Natth Bhamarapavati, the former Rector of Mahidol University (MU), the Vaccine Trial Centre (VTC) was then set up at the Faculty of Tropical Medicine, Mahidol University, Bangkok in February 1984 with the approval of the Ministry of Public Health, Thailand.

The VTC is a clinical facility in the FTM, Mahidol University for testing newly developed vaccines which reach the stage where evaluation in human volunteers is needed. Individual scientists at any national or international institution may have their vaccines tested at this Centre. It is a joint responsibility of Mahidol University and the Ministry of Public Health (MOPH) and operated by the Faculty of Tropical Medicine on their behalf. The establishment of the Centre was started in February 1984, however, full operation was possible around September-October 1986 and the first admission of volunteers into the ward was on 3rd November 1986. The VTC, Bangkok, is the first and the only facility of its kind in Thailand, in the Region and perhaps also in the developing countries. The advantage of conducting vaccine trials at this Centre is that the studies will be on persons residing in an area where the vaccines are going to be utilized most. The knowledge gained will benefit vaccine development and thus lead to effective control of infectious diseases in developing countries.

PHYSICAL FACILITIES

The Centre occupies the 10th and 11th floor of the Chamlong Harinasuta Building of the Faculty of Tropical Medicine with a total area of 648 square meters:

A. Self-contained clinical facilities on the 10th Floor are comprised of:

- twenty bed isolation ward
- sufficient space for recreational activities
- nursing section
- doctor's room and quarters
- laboratories

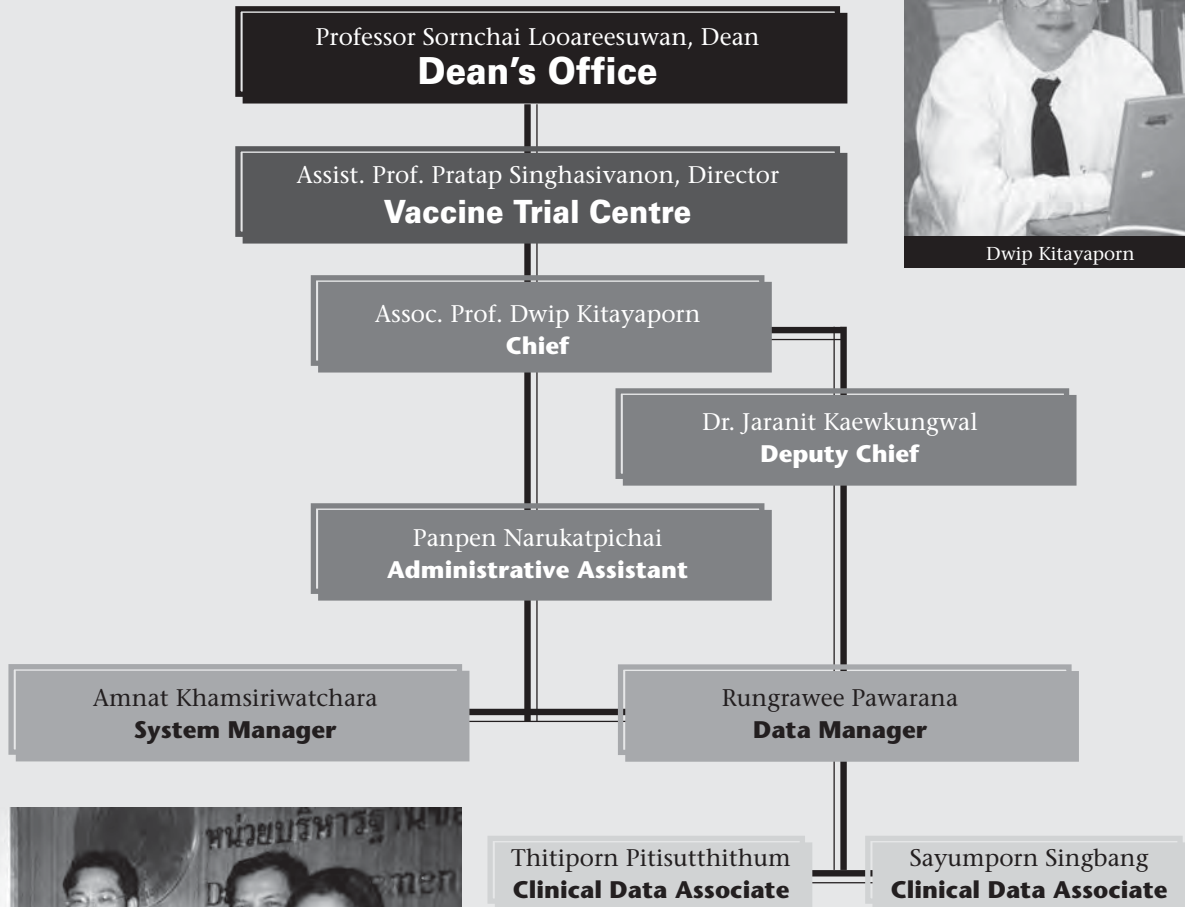
B. Outpatient unit on the 11th floor includes:

- lecture room
- recruitment and screening of volunteers
- follow-up facilities

and also on the 9th floor of the Anek Prasong Building of the Faculty of Tropical Medicine.



DATA MANAGEMENT UNIT Organization Chart



The Data Management Unit or DMU was established in late 1998 and is located on the 9th floor of the Anek Prasong Building, Faculty of Tropical Medicine, to fulfill national requirements under the Thailand National AIDS Committee. Its establishment and the early-year operation have been sponsored by VaxGen Inc., Brisbane, CA, U.S.A.

The primary objective of the Unit is to provide “data management” and “data analysis” services to research projects, particularly clinical trials; meanwhile, its current commitment is put mainly onto the Phase III Trial to determine the efficacy of AIDSVAX™ B/E vaccine in intravenous drug users in Bangkok, Thailand. The personnel structure of DMU is comprised of one Chief (represented by Dr. Dwip Kitayaporn), one Deputy Chief (represented by Dr. Jaranit Kaewkungwal), one Administrative Assistant, one System Manager, one Data Manager and two Clinical Data Associates. The Vaccine Trial Centre (VTC), represented by Dr. Pratap Singhasivanon as the Director, under the Office of the Dean, has designed the DMU to operate as one of its operation arms.

VACCINE TRIAL PROJECTS



Punnee Pitisuttithum

I. HIV VACCINE TRIAL PROJECT:

Principal Investigator:

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Secretary:

- Ms. Saowaluk Thanawatchrangkur
- Ms. Sawanya Sritavil
- Ms. Waraporn Angsuwatkakul

CURRENT RESEARCH ACTIVITIES:

1. A Phase I/II, Double-blind, Placebo-controlled Study of the Chiron Vaccines HIV Thai E gp120/MF59 Vaccine Administered Alone or Combined with the Chiron Vaccines HIV SF2 gp120 Antigen in Healthy HIV-Seronegative Thai Adults

Objective:

- A Phase II Trial of a subtype E-specific gp120 candidate vaccine was carried out in healthy Thai adults to determine safety and immunogenicity

Sites:

- four clinical sites situated within academic centers, 3 in Bangkok and 1 in Chiang Mai

Protocol Summary:

- Vaccine-Chiron Vaccines' recombinant Thai E gp120 protein, adjuvanted with MF59 in 9 dose combinations
- Immunizations-intramuscular injections at 0,1 and 6 months
- Referring to the Thai E, SF2 gp120A dose respectively
are : 25/0 50/0 100/0 25/25 50/50 100/25 25/50 50/50
and : 100/50
- Design-Randomized, double-blind, placebo-control study
- Volunteers are subjects-HIV-seronegative, Thai adults at low risk of HIV exposure

Measures of immunogenicity:

- Binding antibodies to SF2 and Thai E gp120 antigens, measured by enzyme-linked immunosorbent assay (ELISA)
- Neutralizing antibodies to SF2 and Thai E HIV-1, measured by a neutralization assay or an equivalent functional assay

2. A Phase I/II Trial to Evaluate The Safety and Immunogenicity of AIDSVAX™ B/E Vaccine in Bangkok, Thailand**Objective:**

- To evaluate the safety and immunogenicity of three different doses of AIDSVAX™ B/E vaccine (100,300 or 600 µg of each antigen) given at 0,1,6 and 12 months in Thailand

Candidate Vaccine:

- AIDSVAX™ B/E containing MN gp120 and A244 gp120 in aluminum hydroxide adjuvant.

Design:

- Open-label, randomized dose escalation (100 mg, 300 mg and 600 mg of each antigen) given at 0, 1, 6 and 12 months

Population:

- 92 HIV-negative, healthy volunteers, 69 males and 23 females (approximately 30 volunteers in each group)

3. A Phase III Trial to Determine the Efficacy of AIDSVAX™ B/E Vaccine in Intravenous Drug Users in Bangkok, Thailand**Primary Objective:**

- To determine whether immunization with AIDSVAX™ B/E vaccine protects intravenous drug users from HIV-1 infection

Secondary Objective:

- To determine whether prior immunization with AIDSVAX™ B/E vaccine prevents persistent viremia

Other Objectives:

- To evaluate whether immunization with AIDSVAX™ B/E affects the genetic characteristics of HIV-1 “breakthrough viruses”
- To evaluate possible immunologic markers which correlate with protection from HIV-1 infection
- To assess any behavioral effect (positive or negative) associated with participation in a vaccine efficacy trial

4. Phase I/II Trial of Pasteur Merieux Connaught (PMC) Live Recombinant ALVAC-HIV(vCP1521) Priming with Vaxgen gp120 (AIDSVAX™ B/E) Boost in Thai HIV-Seronegative Adults**II. CHOLERA VACCINE TRIAL PROJECT****Validation of a Human Volunteer Challenge Model Using Frozen Bacteria of the New Epidemic Serotype, *V. cholerae* O139 in Thai Volunteers.****Material and Methods:**

Subjects and design of the study

35 Thai volunteers were recruited for an IRB-approved inpatient dose-escalation challenge. The goal was to identify a dose that produced an observed cholera attack are > 80% and an illness of sufficient severity during the defined study period such that the model would be useful for determining vaccine protection. All volunteers were healthy, aged 20-40 years, without a history of clinical cholera or previous cholera vaccination within the past 5 years. To ensure the consent process, volunteers were required to pass a written true-false examination. Volunteers were allocated to serial groups (five each) in such a way that two out of five volunteers had blood group O. Each group was admitted to the VTC isolation ward to receive virulent *V. cholerae* O139 4260B by mouth starting with a dose of 1×10^5 . If the attack rate was less than 4 of 5 or the geometric mean stool volume of the group was < 3L, the study will be repeated with another group with a 10 fold higher dosage (e.g., next dose = 1×10^6), until a clinical attack rate of 90% was obtained. But the dose was not to be administered beyond 10^7 .

Abstracts

VALIDATION OF A HUMAN VOLUNTEER CHALLENGE MODEL USING FROZEN BACTERIA OF THE NEW EPIDEMIC SEROTYPE, *V. CHOLERA* O139: COMPARISON OF THE INOCULUM DOSE RESPONSE BETWEEN NORTH AMERICAN AND THAI VOLUNTEERS

**Punnee Pitisuttithum¹,
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Benjaluck Phonrat¹,
Usanee Suthirarnsunton¹,
Valai Budsalatid¹,
Weerapong Phumratanapapin¹,
Pratap Singhasivanon¹,
Sornchai Looareesuwan¹,
Ralph A Giannella²,
Gilbert M Schiff²,
Bernard Ivanoff³, Dennis Lang⁴**

¹ Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

² Division of Pediatric Gastroenterology and Nutrition and Gamble VTEU, Children's Hospital Medical Center and the University of Cincinnati, OH, USA.

³ World Health Organization, Geneva, Switzerland.

⁴ NIAID, National Institutes of Health, Bethesda, MD USA.

Background: Until recently, all epidemic strains of *Vibrio cholerae* have been of the O1 serotype. Current epidemics have also been caused by a new serotype, O139, synonym Bengal. Although serotype O1 does not confer immunity to the Bengal serotype and no licensed vaccine is available for testing this serotype vaccines, challenge studies with freshly harvested *V. cholerae* O139 organisms have produced variable results between centers. In previously published challenge studies from the Center for Vaccine Development using freshly prepared *V. cholerae* O139, strain A11837, North American volunteers demonstrated an 82% attack rate (purge range 400 mL - 16,500 mL). However, in separate studies even at doses up to 10⁸ CFU in Thai volunteers, using the same freshly prepared strain (A11837), the attack rate never exceeded 1/5 volunteers (purge range 220 mL-3,690 mL). Therefore, prior to beginning multi-center vaccine efficacy studies, we sought to validate the use of a large standardized frozen inoculum of virulent *V. cholerae* O139, strain 4260B.

Methods: A total of 60 volunteers (25 in Cincinnati, Ohio, USA, and 35 in Bangkok, Thailand) were recruited for an IRB-approved inpatient dose-escalation challenge.

Our goal was to identify a dose that produced an observed cholera attack rate $\geq 80\%$ and an illness of sufficient severity during the defined study period such that the model would be useful for determining vaccine protection. Volunteers were challenged in groups of 5 with *V. cholerae* O139 that had been reconstituted immediately before use, with no further incubation or bacterial growth. After challenge, the volunteers were monitored for the development and severity of diarrhea and related symptoms.

Results: In North American volunteers, all 25/25 who were challenged were colonized with *V. cholerae* O139. At a dose of 10⁵ CFU, 8/10 volunteers met the study criteria for diarrhea and had a geometric mean stool volume of 2,175 mL. At a dose of 10⁶ CFU, 14/15 (93%) volunteers experienced purging with a geometric mean stool volume of 5,621 mL (range 1,300-20,300 mL). In Thai volunteers challenge with the identically prepared frozen organisms, 34/35 volunteers became colonized with *V. cholerae* O139. However, at doses up to 10⁶ CFU, only 2/5 or 3/5 volunteers in each group experienced purging; the geometric mean stool volumes at these doses were 1,505-2,355 mL (range 580 mL-4,360 mL). In Thai volunteers challenged at doses $\geq 10^7$ CFU, 11/15 (73%) volunteers experienced purging (range 470-16,020 mL) as shown in Table 1.

Conclusions: In contrast to the freshly prepared challenge strain, in both North American and Thai volunteers, the frozen inoculum model produced an illness with an adequate attack rate and sufficient severity to test the efficacy of new O139 or combined O1/O139 vaccines. However, the challenge dose required to produce an adequate attack rate and disease severity with the identical frozen organism was significantly higher in Thai volunteers than in North American volunteers. This suggests an inherent difference between immunologically naïve North American volunteers and Thai volunteers who may have had prior environmental exposure to *V. cholerae* and/or enterotoxigenic *E. coli*. This observation has potential dosing implications both for future challenge studies and for vaccine trials. ■

Presented at: WS-Japan Conference on Cholera.

HIV-1 VACCINE TRIALS AT THE VACCINE TRIAL CENTRE (VTC), BANGKOK

**Punnee Pitisuttithum¹,
Benjaluck Phonrat¹,
Pravan Suntharasamai¹,
Sricharoen Migasena¹,
Valai Bussaratid¹,
Donald P Francis²,
John Mc Neil³, Arthur Brown⁴,
Anne Marie Duliege⁵**

¹ Vaccine Trial Centre, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

² VaxGen Inc., San Francisco, CA, USA.

³ Walter Reed Army Research Institute (WRAIR).

⁴ Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand.

⁵ Chiron Vaccines.

The first HIV-1 vaccine project at VTC began in 1993 using AIDSVAX™B monovalent vaccine. The vaccine was found to be safe and equally immunogenic in Thai as in the US volunteers. This trial led to the development of combined bivalent B/E vaccines. A Phase I/II trial to evaluate the safety and immunogenicity of AIDSVAX™ B/E vaccine was started in late 1997. Volunteers (n=92) were enrolled from both the general and IVDU population. The results after two doses showed that the vaccine was safe. The study also demonstrated that the immunogenicity of bivalent rgp120 based vaccines is similar to monovalent rgp120 based vaccines. Like monovalent rgp120 vaccines, greater than 95% seroconversion was induced by both of the gp120 antigens at the 6 week time-point. Moreover the magnitude of the antibody response at this time was similar to that obtained with the monovalent vaccine. Based on these results, A

Phase III efficacy trial has been planned in Bangkok and was approved in Jan. 99. At the same time as a part of The Thai AIDS Vaccine Evaluation Group, a trial "A Phase I/II, Double-blind, Placebo-controlled Study of the Chiron HIV Thai E gp120/MF59 Vaccine Administered Alone or Combined with the Chiron HIV SF2 gp120 Antigen in Healthy HIV-Seronegative Thai Adults" was also started. The objectives were to determine the safety and immunogenicity of the vaccine in healthy candidates. VTC is one of 4 sites and has completed enrollment of 99 volunteers including 6 who were in the open label part. 98 have completed the 3 doses immunization. The vaccine was safe, and the immunological results of this study are pending. Thus, the Vaccine Trial Centre of Mahidol University is actively engaged in HIV vaccine, both phase I, II and III. ■

COMMUNITY PARTICIPATION IN HIV-I VACCINE TRIAL IN THAILAND

Punnee Pitisuttithum, Valai Bussaratid, Benjaluck Phonrat, Supa Naksrisook, Wantanee Peonim, Rungrapat Munom, Narumol Tantumnu

The objective of this study was to assess the community interest and participation in HIV-I vaccine trial in Thailand. The results of this will be useful for future HIV-I vaccine efficacy trial in Thailand

A Phase I/II HIV vaccine trial involving general healthy seronegative volunteers was initiated in 1998. Various types of campaign on health education and HIV-1 vaccine trial project were conducted at various institutions.

5 types of campaign were performed within a 5 month period in order to get 98 volunteers interested to

participate in the HIV-I vaccine trial. 834 listened to a brief lecture in a class room or conference room including booth presentation including question and answer after the lecture at universities, colleges and the air force. 451 showed interest in booth or board presentations at the student union; Red Cross fair, blood donor site and Buddhist temples only, about 20 came and sought more information on the trial after listening to the radio or watching TV. Only 159 out of 1285 volunteers really showed their interest and made an appointment for screening, but 151 volunteers did come for the volunteer screening process. 40% of volunteers who came for screening were monks from Buddhist Colleges or monk followers. 84% expressed the reason for participating in the trial as wanting to help the country and society to get HIV-I vaccine for general use.

A brief lecture together with booth presentation followed by question and answer individually or in a group seemed to be the most effective way to find the target population. This procedure can be applied to get the target population for a future vaccine efficacy trial. ■

A PHASE I/II TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF AIDSVAX™ B/E VACCINE IN BANGKOK, THAILAND - PRILIMINARY RESULTS

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Suwane Raktham²,
La-ong Srisuwanvilai²,
Dwip Kittayaporn¹,
Jaranit Kaewkangwal¹,
Sricharoen Migasena¹,
Krit Hiranrus², P Berman¹,
D Francis³**

¹ Vaccine Trial Centre Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

² Department of Health Bangkok Metropolitan Administration, Thailand.

³ Vaxgen Inc. San Francisco, USA.

OBJECTIVE: To evaluate the safety and immunogenicity of three different doses of AIDSVAX™ B/E vaccine 100, 300 or 600 µg of each antigen) given at 0, 1, 6 and 12 months in Thailand.

DESIGN: Open-label, randomized dose escalation (100 µg, 300 µg and 600 µg of each antigen)

Population: 90 HIV-negative, healthy volunteers (30 volunteers in each group)

SAFETY: Safety assessments are conducted 1 hr, 3 days and 14 days after each immunization.

IMMUNOGENICITY: Overall immunogenicity is evaluated by measuring antibody titers to gp120 at baseline, prior to and two weeks following each immunization. Antigen-specific immunity is evaluated by measuring antibody titers to a V2 peptide.

RESULTS Reactogenicity: The vaccine was well tolerated. Pain and tenderness at the injection site were

the most commonly reported symptoms across all dose groups. Most reactogenicity symptoms reported were self-limiting and typically resolved within 14 days of onset. However, pain and tenderness appeared to increase with escalating doses (26.7% of subjects at the 100 µg dose group, as compared to 66.7% and 55.2% of subjects at the 300 µg and 600 µg dose groups).

Month 1.5 Immunogenicity: Greater than 95% seroconversion was detected to all of the gp120 antigens at the 6.5 month time-point. When antigen specificity was examined, it was found that peptides from the V2 domains of the three envelope glycoprotein antigens clearly distinguished antibodies to each antigen. These antigen specific immune responses were dose dependent.

Month 6.5 Immunogenicity: Both MN-rgp120 and A244-rgp120 titers approach maximum values after two immunizations whereas MN V2 titers continue to increase (two to three-fold) after the third (6.5 month) immunization with the mean optical density values for the 600, 300 and 100 µg dose groups were 0.545, 0.248 and 0.069, respectively at the 1.5 month timepoint and 1.202, 0.570, and 0.213, respectively at the 6.5 month timepoint. ■

AIDSVAX B/E Vaccine is highly safe and immunogenic as AIDSVAX™ MN monovalent vaccine. Together with previous evidence the phase III efficacy trial of AIDSVAX™ B/E Vaccine was initiated this year in Thailand.

SPECIES OF CANDIDA IN ORO-PHARYNGEAL CANDIDIASIS IN HIV AIDS PATIENTS IN THAILAND - PRELIMINARY RESULT

**Valai Bussaratid,
Punnee Pitisuttithum,
Somsit Tansuphaswadikul,
Benjaluck Phonrat, Paul Howe,
Nicholas J White**

Objective: To determine the prevalence of various species of *Candida* in oro-pharyngeal candidiasis (OPC) in HIV AIDS patients in Thailand.

Methods: After the confirmation of OPC by KOH preparation, the samples were cultured and species of *Candida* were identified.

Results: Nineteen of 23 cases (83%) were singularly infected with *C. albicans*. Four cases (18%) had mixed infections between *C. albicans* and *C. glabrata*. *C. albicans* was predominant in 2 cases while in the other two cases, the predominant infection was *C. glabrata*.

Conclusion: The finding that *C. albicans* is the most prevalent species in OPC in HIV which is similar to other studies. Other species that have been known to coinfect *C. albicans* include *C. krusei* and *C. lipotica*. The study continues for another 8 months. ■

EXPERIENCE TO DATE WITH VACCINE TRIAL IN RECOVERING INTRAVENOUS DRUG USERS IN BANGKOK: LESSON FOR THE FUTURE

**Punnee Pitisuttithum¹,
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Suvanee Raktham², et al.**

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² Bangkok Metropolitan Administration, Bangkok, Thailand.

Objectives: to describe the issues of knowledge, consent process and follow-up of volunteers who participated in HIV-1 vaccine trials.

Methods: 33 recovering intravenous drug users who volunteered for vaccine trial were informed in depth about the vaccine trial procedures and interviewed using behavior questionnaires. 20 true-false questions must be passed before signing the consent form. All volunteers were followed as planned in the protocol (M0 M1 M1.5 M6 M6.5 M12 M12.5 M18). At the end of the study all of them were asked to

answer questionnaires about the project and problems encountered during the study period and 16 of them were randomly selected to perform again the 20 true-false questions (as used before signing the consent form) to ensure their proper understanding of the project.

Results: Consent comprehension. There were two of the 20 true-false questions often misunderstood by nearly half of the volunteers. One of the subjects wanted more details on the volunteers who had participated in the similar vaccine trial in U.S.A. At the end of the study, of the 16 who were randomly selected to repeat the true-false examination, 10 had improved scores, and none scored less than what they achieved before the trial.

Attitude towards the vaccines: 70% felt that successful vaccine was likely, 91% believed that this vaccine is effective but all agreed to minimize their risk behaviors. However, 40% of them were still afraid that vaccine may enhance disease progression.

Follow up issue: 3 out of 33 were found to have positive urine opiates and were excluded from the study. 100% follow-up was achieved during the study period of 18 months, even though 4 of them had been incarcerated at times during the study. Two had road accidents with prolonged hospitalization. Of the 30 volunteers who replied to the questionnaire at the end of the project, 23 said they will advise their friends to join further studies if there are any in the future. ■

Presented at: The 4th International Congress on AIDS in Asia and the Pacific, October 25-29, 1997 Philippines.

CLINICAL RESPONSE TO HIV THAI E / MF59 VACCINE ADMINISTERED ALONE OR COMBINED WITH SF2 GP 120 ANTIGEN IN HEALTHY VOLUNTEERS

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² RIHES, Chiang Mai University, Chiang Mai, Thailand.

Objective: To determine the safety of three doses of HIV Thai E gp120/MF59 vaccine alone or combined with SF2 gp 120 antigen in healthy HIV-1 seronegative Thai adults.

Design: Open-labeled, dose escalating study.

Method: Groups of three healthy HIV seronegative volunteers were sequentially block enrolled to one of 4 antigen/dose combinations: 25 ug of Thai E gp120/MF59 (Group I), 25 ug of Thai E gp120/MF59+25 ug SF2 gp120/MF59 (Group II), 100 ug of Thai E gp120/MF59 (Group III) and 100 ug of Thai E gp120/MF59+50 ug SF2 gp120/MF59

(Group IV). Sequential enrollment to each group was separated by 48 hrs and required that the preceding group be free of serious reactogenic reactions. Immunizations were given at 0, 1, 6 months. All volunteers were evaluated 24-48 hours after vaccination and were required to record daily symptoms for 6 days post immunization. Up to the time of submission of abstract, only two doses of vaccination have been administered.

Results: Reported local and systemic symptoms by vaccine dose and number of vaccinations.

Group I		
1st Vac	2nd Vac	Group II
1st Vac	2nd Vac	Group III
1st Vac	2nd Vac	Group IV
1st Vac	2nd Vac	

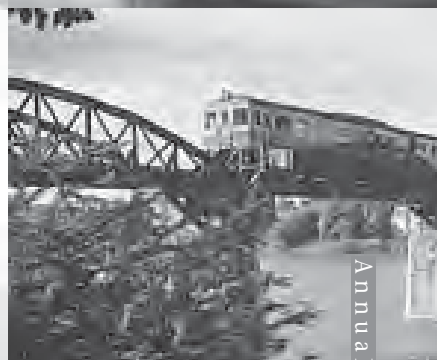
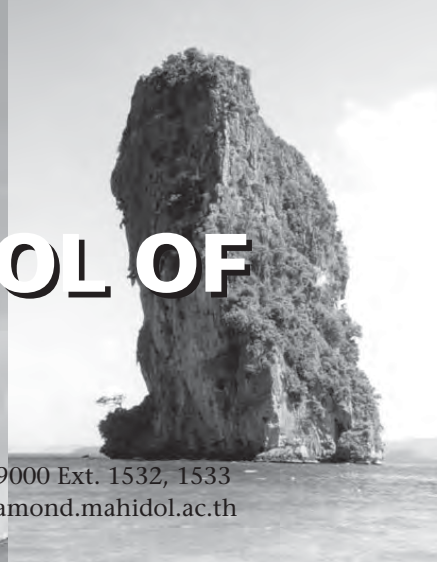
Pain at injection site	2/3	1/3	3/3	3/3	3/3	3/3	3/3	3/3
Warmth at injection site	1/3	0/3	0/3	0/3	2/3	0/3	1/3	1/3
Malaise	0/3	0/3	1/3	2/3	0/3	1/3	1/3	0/3
Fever (> 38 OC)	0/3	0/3	0/3	1/3	0/3	0/3	0/3	0/3

Conclusion: Thai E gp120/MF59 vaccine administered alone or combined with SF2 gp 120 antigen appears to be safe. No serious adverse events have been observed following two immunizations. ■

Presented at: The 12th World AIDS Conference; 1998 Jun 28-Jul 3 Geneva, Switzerland.

THE BANGKOK SCHOOL OF TROPICAL MEDICINE

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The Bangkok School of Tropical Medicine, Faculty of Tropical Medicine, Mahidol University was established in 1960 to teach Thai medical doctors, especially those who work in rural areas, tropical medicine, parasitology and the preventive aspects of endemic diseases. The course leading to the Diploma in Tropical Medicine and Hygiene (D. T. M. & H.) organized as an international course since 1967, with the establishment of the SEAMEO Regional Tropical Medicine and Public Health Project, and the designation of the Faculty as the TROPMED National Centre of Thailand. Lectures are given in English and the courses are open to students from other countries around the world. Since its inception, class sizes have steadily increased. The original curriculum was based on the D.T.M.&H. course conducted by the Liverpool School of Tropical Medicine, and has been modified to provide adequate orientation towards preventive medicine, endemic health problems of Thailand, and public health problems in other countries of Southeast Asia. The Bangkok School of Tropical Medicine has been extended to provide continuing education to doctors, research workers, medical personnel and professionals concerned with tropical medicine and public health. The degree in Tropical Medicine, instituted internationally, was offered at the M.Sc. level in 1967 and at the Ph.D level in 1975. The basic intent was to provide a multidisciplinary approach to graduate training. Master and Doctorate degree programmes in Clinical Tropical Medicine were first offered to medical doctors in 1982 and 1995, respectively. The curricula of the programmes were revised and offered regularly as follows:



REGULAR POSTGRADUATE PROGRAMMES

1. Graduate Diploma in Tropical Medicine and Hygiene (D.T.M.&H.)

The course provides participating medical doctors with the concepts and principles of the clinical management of tropical diseases, epidemiology, prevention and control of tropical diseases and health problems in Southeast Asia. Students gain experience with case demonstrations and field trips to hospitals in rural areas of Thailand. The duration of the course is six months, running from April to September.

2. Master of Science in Tropical Medicine (M.Sc.(Trop. Med.))

The programme provides appropriate knowledge and skills for competency in research, and the capacity to deliver technical services related to tropical medicine. Course duration is approximately two years, which includes a minimum of 24 credits for coursework and 12 credits for thesis. The programme offers 14 major fields for students to choose from according to their needs and future work, as follows: Clinical Tropical Medicine, Clinical Pharmacology, Epidemiology, Microbiology, Immunology, Biochemical Nutrition, Nutritional Epidemiology, Nutritional Toxicology, Tropical Pathology, Radiological Science, Social Medicine, Environmental Toxicology, Environmental Health, Parasitology and Medical Entomology. Applicants who are qualified to enrol in this programme are those who have graduated with an M.D., D.D.S., D.V.M. Pharmacy, or B.Sc. degree.

3. Doctor of Philosophy in Tropical Medicine (Ph.D. (Trop. Med.))

The doctoral programme provides advanced knowledge and skills for competency in research, particularly in Tropical Medicine, which includes the research programme (Plan 1) and the regular programme (course work and research) (Plan 2). Students are able to choose one major field in Tropical Medicine according to their needs and future work, as follows: Clinical Tropical Medicine, Clinical Pharmacology, Epidemiology, Microbiology, Immunology, Biochemical Nutrition, Nutritional Epidemiology, Nutritional Toxicology, Tropical Pathology, Radiological Science, Social Medicine, Environmental Toxicology, Environmental Health, Parasitology and Medical Entomology. Length of study is approximately three years. Applicants who are qualified to enrol in this programme are those who have graduated with an M.D., D.D.S., D.V.M., M.Sc., or B.Sc. (Hons) degree.

4. Master of Clinical Tropical Medicine ((M.C.T.M.) and (M.C.T.M. (Trop. Ped.))

The M.C.T.M. programme has been established to train medical doctors to be :

- well-versed and well-informed in tropical and endemic diseases with special reference to Southeast Asia, in relation to their causes, epidemiology, pathogenic mechanisms, prevention and control.
- able to efficiently examine, diagnose and treat patients suffering from tropical and endemic diseases. In the major field of Clinical Tropical Medicine, students study abnormalities mainly in adults, while in the major field of Tropical Pediatrics, students study only abnormalities in children.
- able to give consultative advice, disseminate and impart knowledge of tropical medicine.
- able to conduct clinical research.

The programme consists of coursework and thesis. Students will conduct clinical research and gain clinical experience at a Regional Hospital of the Ministry of Public Health in a province of Thailand. The duration of the programme is one year, from April to March.

5. Doctor of Philosophy in Clinical Tropical Medicine (Ph.D. (Clin. Trop. Med.))

The Ph.D. (Clin. Trop. Med.) programme has been established for medical doctors to gain advanced knowledge and study new techniques, and apply them to areas of research in clinical tropical medicine. Students are required to conduct an extensive research project related to clinical tropical medicine which should be original work. The minimum length of study is three years.

Candidates are required to have graduated with a M.C.T.M. degree or have been certified in clinical specialties by the Board of the Thai Medical Council or its equivalent and hold the D.T.M.&H., or hold a licence for general medicine in their domicile country or in the country where they graduated.

The Faculty of Tropical Medicine, Mahidol University has been the SEAMEO TROPMED Regional Centre for Tropical Medicine since 1994. Much of the School's good reputation overseas derives from its education and training activities. Students enrolled in its programmes originate from SEAMEO member countries and other countries (Thailand, Indonesia, the Philippines, Malaysia, Lao PDR, Cambodia, Myanmar, Vietnam,

Singapore, Bangladesh, India, Japan, Pakistan, Afghanistan, Nepal, Iran, Sri Lanka, Australia, the People's Republic of China, Papua New Guinea, New Zealand, Germany, Sweden, Switzerland, Norway, Austria, Spain, Denmark, Italy, Finland, France, the Netherlands, the United Kingdom, Somalia, Yemen, Tanzania, Palestine, Croatia and the U.S.A.).



COLLABORATIVE TRAINING PROGRAMMES

1. Master of Clinical Tropical Pediatrics Bangkok/Liverpool Collaboration

The Faculty of Tropical Medicine, Mahidol University and the Liverpool School of Tropical Medicine collaborate in the teaching and training of postgraduates in both institutions registered for Master's Courses in Tropical Pediatrics, but each university issues its own degree in accordance with its own degree regulations. Candidates registered for the Master's Course(s) in Liverpool commence their training in Liverpool (3-4 months) and are provided with clinical and field experience in Thailand for a period of 3 months between April and August to gain practical experience of tropical pediatrics which cannot be provided in Liverpool, in parasitic diseases (eg. malaria, hookworm infection, strongyloidiasis, giardiasis, ascariasis, liver fluke infection, gnathostomiasis, angiostrongyloidiasis, paragonimiasis, cysticercosis etc.) and other infectious diseases (eg. dengue hemorrhagic fever, Japanese encephalitis, tuberculosis, meningitis, leptospirosis, rabies, etc.). Master's candidates in Bangkok may be sent to Liverpool for clinical or field experience but this is not a pre-requisite of this agreement.



2. Austrian Diploma in Tropical Medicine

The Austrian Society of Tropical Medicine and Parasitology and the Faculty of Tropical Medicine, Mahidol University have jointly offered an annual programme leading to the Austrian Diploma in Tropical Medicine since 1992. The 4-month programme, starting in January, focuses on tropical diseases and enables medical doctors to understand the clinical, biological, epidemiological and social dimensions of tropical diseases, particularly in Southeast Asia. After participants have attended lectures for 3 months in Austria, they continue attending for more clinical experience for 1 month in Thailand at the Faculty of Tropical Medicine, Mahidol University. Apart from lectures, participants also have the opportunity to see many patients suffering from tropical diseases at the Hospital for Tropical Diseases and other hospitals in Bangkok and in the northeast of Thailand. This programme is directed by Professor Franz Ambrosch and the clinical part is organized by Professor Walter Wernsdorfer and Assoc. Prof. Wichai Supanaranond.

The objectives of the course are :

- (1) To provide participating medical doctors with clinical experience and a better understanding of health problems at the community level in Southeast Asia and to increase their ability to cope with them.
- (2) To promote a better understanding of the culture and way of life of people in Southeast Asia, leading to closer cooperation in dealing with regional health problems.

3. Master of Science in Clinical Epidemiology

The Faculty of Tropical Medicine, in collaboration with the Faculty of Public Health and the Faculty of Medicine, Ramathibodhi Hospital, Mahidol University, organizes an international programme leading to the Master of Science in Medical Epidemiology. The course focuses on the development of epidemiological skills and competency for doctors, especially in the countries of Southeast Asia, in the field of clinical or community epidemiology and also in health service research. The ultimate objective of this programme is to provide academic and health service leadership, which will facilitate effective performance of public health and medical care programmes at every level in various countries. The length of study is one year, six months for coursework and six months for the Master's thesis.



D.T.M. & H. 1999

Dr. Buthsaraporn Surakhaka	Thailand	Miss Piyaporn Suebtrakul	Thailand
Dr. Karnchana Pornpininworakij	Thailand	Mrs. Phimon Sri Saengkar	Thailand
Dr. Phommady Vesaphong	Thailand	Miss Malida Soontornruengyot	Thailand
Dr. Vanintorn Sultornsanee	Thailand	Miss Ratchanok Kumsiri	Thailand
Dr. Harald Noedl	Austria	Miss Risara Jakswan	Thailand
Dr. Md. Zahangir Alam	Bangladesh	Miss Wandee Sawatmongkonkun	Thailand
Dr. Shaibal Barua	Bangladesh	Miss Somrak Jestakhom	Thailand
Dr. Prom Phanit	Cambodia	Mr. Sumate Aumpawong	Thailand
Dr. Tep Navuth	Cambodia	Miss Suwanee Sungkawasee	Thailand
Dr. Buor Vatha	Cambodia	Miss Souwanit Nakasiri	Thailand
Dr. Yuki Ishihara	Japan	Mr. Apichai Srijan	Thailand
Dr. Darachith Sukhaseum	Lao P.D.R.	Mr. Ram Chandra Silwal	Nepal
Dr. Sinthavong Phyathep	Lao P.D.R.	Dr. Lek Dysoley	Cambodia
Dr. Sodalay Onnavong	Lao P.D.R.		
Dr. Nanthakone Sihapanya	Lao P.D.R.	2nd year students	
Dr. Lintha Mithkeopanya	Lao P.D.R.	Pol. Lt. Kitiyaporn Chaichana	Thailand
Dr. Somchith Inthavongsack	Lao P.D.R.	Miss Chuthaporn Toonboonchoo	Thailand
Dr. Wong Lee Kang	Malaysia	Mrs. Tippayarat Yoonuan	Thailand
Dr. Thuang Hlaing	Myanmar	Miss Bunguorn Sermsart	Thailand
Dr. Hla Yin Myint	Myanmar	Mr. Pornchai Kirdsiri	Thailand
Dr. Thein Win	Myanmar	Miss Yupa Nakkinkun	Thailand
Dr. Umar Zada	Pakistan	Miss Varangkana Visermanee	Thailand
Dr. Michael Angelo L. Wambangco	Philippines	Miss Waraporn Chaimchitpanid	Thailand
Dr. Maxim Berdnikov	Russia	Miss Wacharee Tiyasuttiapan	Thailand
Dr. Le Quoc Hung	Vietnam	Miss Suwaporn Anantrakulsin	Thailand
Dr. Phan Trong Giao	Vietnam	Miss Akanitt Jittmittraphap	Thailand
Dr. Nguyen Manh Tuan	Vietnam	Mr. Apichai Supasansatorn	Thailand
Dr. Nguyen Thi Thanh Binh	Vietnam	Miss Umaporn Pinyosirikul	Thailand
Dr. Dinh Xuan Huong	Vietnam	Mr. Ferdinand V. Salazar	Philippines
Dr. Daniel Rikleen	U.S.A.		
Dr. Kristin Lobo	U.S.A.	3rd year students	
Dr. Kent Copeland	U.S.A.	Mrs. Kesaree Chewachatrekasem	Thailand
Dr. Diana C. Dorn	U.S.A.	Miss Napa Onvimala	Thailand
Attended		Miss Watcharee Saisongkorh	Thailand
Mr. Yoshiro Nagao	Japan	Miss Sunthareeya Waicharoen	Thailand

M.C.T.M. 1998-1999

Dr. Aung Myat Oo	Myanmar
Dr. Minn Minn Soe	Myanmar
Dr. Nyunt Naing	Myanmar
Dr. Achuyt Bhattarai	Nepal
Dr. Somboun Bounyadeth	Lao P.D.R.
Dr. Chong Tse David Tan	Singapore
Dr. Michio Ono	Japan

M.SC. (TROP. MED.) 1999

1st year students	
Miss Kanjana Sonji	Thailand
Miss Gaysorn Bunyaraksyotin	Thailand
Miss Junpen Suwimonteerabutr	Thailand
Mr. Narong Nitatpattana	Thailand
Miss Nahathai Chulakarat	Thailand
Lt. Tossapon Chaiyasith	Thailand
Miss Thanida Tangwanicharoen	Thailand
Mr. Tanett Pakeetoot	Thailand

5th year students	
Mrs. Montakarn Vongpakorn	Thailand

PH.D. (TROP. MED.) 1999

1st year students	
Miss. Naowarut Dechkum	Thailand
Mr. Kamon Foihirun	Thailand
Miss Chutima Kamkhaek	Thailand

PH.D. (TROP. MED.) 1999 (Continued)**1st year students** (continued)

Miss Nantika Panutdaporn	Thailand
Mrs. Prapa Nunthawarasilp	Thailand
Mr. Piyanan Taweethavonsawat	Thailand
Mr. Panas Thumkiratiwong	Thailand
Miss Pornphan Diraphat	Thailand
Miss Pattra Suntornthiticharoen	Thailand
Miss Pinnarat Pengkoom	Thailand
Mr. Yuttana Sudjaroen	Thailand
Mrs. Ratee Leelawongtawon	Thailand
Miss Rungpetch Khaengraeng	Thailand
Miss Waraphon Phimpraphi	Thailand
Miss Walairut Tuntaprasart	Thailand
Miss Suwalee Tantawiwat	Thailand
Mrs. Oranan Prommano	Thailand
Mr. Preecha Liangpunsakul	Thailand
Miss Duangkamol Viroonudomphol	Thailand
Mr. Hari Har Joshi	Nepal
Mr. Rajendra Kumar B.C.	Nepal

2nd year students

Miss Surangrat Srisurapanon	Thailand
Miss Kriyaporn Songmuaeng	Thailand
Miss Kleebkaew Pitasawad	Thailand
Miss Charinthon Ngamamonpirat	Thailand
Mrs. Prapin Tharnpoophasiam	Thailand
Miss Pungasem Paeporn	Thailand
Miss Mallika Imwong	Thailand
Mr. Mana Vatakul	Thailand

Mrs. Yupadee Sirissinsuk	Thailand
Miss Wanida Pongstaporn	Thailand
Miss Sawanee Tengrungsun	Thailand
Miss Nitchakarn Noranate	Thailand
Miss Pittayaporn Moungrnoi	Thailand
Miss Wannaporn Ittiprasert	Thailand
Miss Yuwadee Trongtokit	Thailand
Dr. Mayfong Mayxay	Lao P.D.R.

3rd year students

Mrs. Kanjana Hongtong	Thailand
Mrs. Kamolrat Silamut	Thailand
Mrs. Chantima Lohachit	Thailand
Mr. Chamnarn Apiwathnasorn	Thailand
Mr. Polrat Wilairatana	Thailand
Mr. Paron Dekumyoy	Thailand
Mr. Apichart Nantprasert	Thailand
Miss Urai Chaisri	Thailand
Miss Usavadee Thavara	Thailand
Mrs. Emsri Pongponrat	Thailand
Mrs. Patcharin Saengjaruk	Thailand
Miss Siriwan Chancharoen	Thailand
Miss Thitima Wongsaroj	Thailand

4th year students

Mr. Ruangyuth Chaiworaporn	Thailand
Dr. Le Thi Diem Thuy	Vietnam

5th year students

Miss Roongrasamee Soisangwan	Thailand
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THESIS TITLES**M.C.T.M.**

Department	Name	Title of Thesis	Advisor
Clinical Tropical Medicine	Dr. Achuyt Bhattaria	Drug resistant tuberculosis in patients with AIDS at Bamrasnaradura Hospital	Prof. Sasithon Pukrittayakamee
Clinical Tropical Medicine	Dr. Aung Myat Oo	Drug resistant tuberculosis in patients with AIDS at Bamrasnaradura Hospital	Assoc. Prof. Punnee Pitisuttithum
Clinical Tropical Medicine	Dr. Minn Minn Soe	Drug resistant tuberculosis in patients with AIDS at Bamrasnaradura Hospital	Prof. Polrat Wilairatana
Clinical Tropical Medicine	Dr. Somboun Bounyadeth	Cutaneous findings in HIV positive patients at Pramongkutklao Hospital Skin Clinic	Prof. Swangjai Pungpak
Clinical Tropical Medicine	Dr. Nyunt Naing	Cutaneous findings in HIV positive patients at Pramongkutklao Hospital Skin Clinic	Assoc. Prof. Wichai Supanaranond
Clinical Tropical Medicine	Dr. Chong Tse David Tan	Cutaneous findings in HIV positive patients at Pramongkutklao Hospital Skin Clinic	Prof. Swangjai Pungpak

M.SC. (TROP. MED.)

Department	Name	Title of Thesis	Advisor
Clinical Tropical Medicine	Mr. Wick Banmairuoy	Development of a high performance liquid chromatographic method for determination of mycophenolic acid in biological fluids and preliminary investigation of its pharmacokinetics in Thai recipients of kidney transplantation	Assoc. Prof. Wichai Supanaranond
Clinical Tropical Medicine	Miss Oumaporn Thasanor	Development of an <i>in vitro</i> test system for the assessment of <i>Plasmodium vivax</i> susceptibility to antimalarial drugs	Assoc. Prof. Wichai Supanaranond
Helminthology	Miss Montakan Yongpakorn	Evaluation of immune-reaction between excretory-secretory and partially purified somatic antigens of <i>Fasciola gigantica</i> and cattle sera by Lat, ELISA and Immunoblot	Assoc. Prof. Jitra Waikagul

M.SC. (TROP. MED.) (Continued)

Department	Name	Title of Thesis	Advisor
Helminthology	Col. Lt. Kitiyaporn Chaichana	Partial purification of <i>Bithynia siamensis</i> glomomphalus snail proteins as antigens for diagnosis of human opisthorchiasis by ELISA and immunoblot	Assoc. Prof. Jitra Waikagul
Helminthology	Mrs. Tippayarat Yoonuan	Experimental study on life-cycle of <i>Spiromate</i> sp. in Thailand	Assoc. Prof. Jitra Waikagul
Microbiology and Immunology	Mrs. Kesaree Chewachatrekasem	The multistage character of immunity to <i>Plasmodium falciparum</i> antigens in naturally exposed malaria endemic population	Prof. Srisin Khusmith
Microbiology and Immunology	Dr. Tran Do Hung	Epidemiology study of beta hemolytic streptococcus group A in the pharynx of school children in Cantho Province, Vietnam	Assist. Prof. Usanee Suthisarnsuntorn
Microbiology and Immunology	Miss. Watcharee Saisongkorh	DNA amplification for <i>V. cholerae</i> O:139 detection	Assoc. Prof. Pramuan Tapchaisri
Microbiology and Immunology	Miss. Sriprai Yenyam	Development of new diagram for simple diagnosis of non-fermentative gram negative bacteria	Assist. Prof. Usanee Suthisarnsuntorn
Microbiology and Immunology	Miss. Sunthareeya Waicharoen	Simple and rapid detection of scrub typhus	Dr. Varee Prasertsiriroj
Microbiology and Immunology	Miss. Searmsap Riengrod	A rapid direct-agent detection system for <i>Orientia tsutsugamushi</i>	Dr. Varee Prasertsiriroj
Microbiology and Immunology	Miss. Saowaluk Julnimi	Diagnosis of pertussis using MAb-based dot-blot ELISA, indirect ELISA and DNA amplification	Assoc. Prof. Manas Chongsa-nguan
Microbiology and Immunology	Miss Bunuorn Sermsart	Diagnosis of trichinellosis using specific antigen purified from monoclonal antibody affinity chromatography	Prof. Wanpen Chaicumpa
Microbiology and Immunology	Miss Yupa Nakkinkun	Platelet dysfunction in immune thrombocytopenic disorder	Prof. Wanpen Chaicumpa
Microbiology and Immunology	Miss Wacharee Tiyasuttipan	Genetic analysis of <i>Vibrio cholerae</i> isolated in Thailand for epidemic tracing	Assoc. Prof. Pramuan Tapchaisri

M.SC. (TROP. MED.) (Continued)

Department	Name	Title of Thesis	Advisor
Microbiology and Immunology	Miss Akanitt Jittmittraphap	Detection of dengue viral RNA in patient sera by nucleic acid sequence-base amplification (NASBA) and comparison with polymerase chain reaction (PCR)	Assoc. Prof. Wipawee Usawattanakul
Microbiology and Immunology	Mr. Apichai Supasansatorn	Towards the monoclonal antibodies to filamentous hemagglutinin of <i>Bordetella pertussis</i>	Assoc. Prof. Manas Chongsa-nguan
Microbiology and Immunology	Miss. Usa Boonsathorn	Cloning and expression of gene encoding hepatitis B core virus antigen in yeast	Assoc. Prof. Surang Tantivanich
Protozoology	Miss Chutamas Koomrungrueng	The correlation of <i>in-vivo</i> and <i>in-vitro</i> sensitivity of anti-malarial drugs	Assist. Prof. Porntip Petmitr
Social and Environmental Medicine	Mr. Pornchai Kirdsiri	Risk behavioral surveillance of sex-worker in Kanchanaburi Province	Dr. Jaranit Kaewkungwal
Social and Environmental Medicine	Miss Varangkana Visermanee	-	Assist. Prof. Ladda Tangbanluekal
Social and Environmental Medicine	Miss Waraporn Chaimchitpanid	-	Assist. Prof. Ladda Tangbanluekal
Tropical Nutrition and Food Science	Miss. Napa Onvimala	Application of reverse transcriptase polymerase chain reaction for identification of rotavirus serotypes	Assoc. Prof. Supranee Changbumrung
Tropical Nutrition and Food Science	Miss. Siriwan Tribanyatkul	Serum leptin concentration in human obese subjects	Assoc. Prof. Rungsumn Tungtrongchitr
Tropical Nutrition and Food Science	Mrs. Aimmanas Attawish	Cytotoxic and mutagenic tests of medicinal plants	Assoc. Prof. Supranee Changbumrung
Tropical Nutrition and Food Science	Miss Chuthaporn Toonboonchoo	B ₁₂ folic acid and hematological status of overweight and obese Thai in Bangkok	Assoc. Prof. Rungsumn Tungtrongchitr
Tropical Nutrition and Food Science	Miss Umaporn Pinyosirikul	-	Assoc. Prof. Supranee Changbumrung
Tropical Pathology	Miss Suwaporn Anantrakulsin	Hematopoietic features of the bone marrow of <i>Plasmodium falciparum</i> -infected patients	Assist. Prof. Yaowapa Maneerat
Clinical Tropical Medicine	Dr. Mayfong Mayxay	<i>In vivo</i> and <i>in vitro</i> studies in acute malaria	Prof. Sasithon Pukrittayakamee

Ph.D. (TROP. MED.)

Department	Name	Title of Thesis	Advisor
Clinical Tropical Medicine	Mrs. Kamolrat Silamut	The relationship between the morphology of <i>Plasmodium falciparum</i> parasites, antimalarial treatment and pathology in falciparum malaria	Prof. Sasithon Pukrittayakamee
Clinical Tropical Medicine	Dr. Polrat Wilairatana	Prognostic significance of skin sequestration of <i>Plasmodium falciparum</i> -infected erythrocytes in severe malaria	Prof. Sornchai Looareesuwan
Clinical Tropical Medicine	Mr. Apichart Nontprasert	Neurotoxicity of antimalarial drugs in animal model	Prof. Sasithon Pukrittayakamee
Clinical Tropical Medicine	Dr. Yupaporn Wattanakoon	The role of clinical pharmacology in the treatment of tropical diseases	Assoc. Prof. Wichai Supanaranond
Clinical Tropical Medicine	Dr. Yoshinari Moriyama	–	Prof. Sornchai Looareesuwan
Clinical Tropical Medicine	Mrs. Emsri Pongponrat	Ultrastructural studies of <i>Plasmodium falciparum</i> in human organs the interactions between the parasitized erythrocytes and the host cells	Prof. Sornchai Looareesuwan
Clinical Tropical Medicine	Dr. Le Thi Diem Thuy	Clinical pharmacology of the combination of artemether and proquanil	Prof. Sornchai Looareesuwan
Clinical Tropical Medicine	Miss Mallika Imwong	Genotyping of <i>Plasmodium vivax</i>	Prof. Sasithon Pukrittayakamee
Helminthology	Mr. Paron Dekumyoy	Cloning of antigenic gene from female <i>Angiostrongylus cantonensis</i> adult worms	Assoc. Prof. Jitra Waikagul
Helminthology	Miss. Charinthon Ngamamonpirat	<i>Trichinella spiralis</i> in Thailand: differentiation of isolates by polymerase chain reaction (PCR) method	Assoc. Prof. Jitra Waikagul
Medical Entomology	Mr. Chamnarn Apiwathnasorn	Some promising phytochemical Thai plants for control of mosquito vectors	Assist. Prof. Achara Asavanich
Medical Entomology	Miss. Usavadee Thavara	Ecological studies of dengue mosquito vectors in four provinces of Southern Thailand	Assist. Prof. Narumon Komalamisra
Medical Entomology	Miss Yuwadee Trongtokit	–	–

Ph.D. (TROP. MED.) (Continued)

Department	Name	Title of Thesis	Advisor
Medical Entomology	Miss Pungasem Paeporn	Insecticide resistance in <i>Aedes aegypti</i> and the significance to its biochemistry and genetics	Assoc. Prof. Vanida Deesin
Microbiology and Immunology	Miss. Roongrasamee Soisangwan	Rapid diagnosis of shigellae	Prof. Wanpen Chaicumpa
Microbiology and Immunology	Ms. Wannaporn Ittiprasert	Towards specific diagnosis of <i>Schistosoma mekongi</i> infection	Prof. Wanpen Chaicumpa
Microbiology and Immunology	Miss. Urai Chaisri	Pathology of enterohemorrhagic <i>Escherichia coli</i> : infection and protective role of monoclonal antibodies against O-antigen and Shiga-like toxin(s)	Prof. Wanpen Chaicumpa
Microbiology and Immunology	Miss. Patcharin Saengjaruk	–	Prof. Srisin Khusmith
Microbiology and Immunology	Miss. Thitima Wongsaroj	–	Prof. Wanpen Chaicumpa
Microbiology and Immunology	Miss. Surangrat Srisurapannon	Characterization of B cell-epitope of HIV-1 subtype E	Prof. Srisin Khusmith
Microbiology and Immunology	Miss Nitchakarn Noranate	–	–
Social and Environmental Medicine	Miss Yupadee Sirisinsuk	–	Assist. Prof. Ladda Tangbanluekan
Social and Environmental Medicine	Mrs. Chantima Lohachit	Ecological studies of <i>Bithynia goniomphalos</i> a snail intermediate host of <i>Opisthorchis viverrini</i> in Northeast Thailand	Assoc. Prof. Viroj Kitikoon
Social and Environmental Medicine	Mr. Ruangyuth Chaiworaporn	Studies on <i>Schistosoma spindale</i> Montgomery, 1906 (Trematoda: Schistosomatidae) and related taxa, the causative agent of bovine schistosomiasis in Thailand	Assoc. Prof. Viroj Kitikoon
Social and Environmental Medicine	Mrs. Prapin Tharnpoophasiam	–	Assist. Prof. Ladda Tangbanluekal
Social and Environmental Medicine	Mrs. Kleebkaew Pitasawad	–	Assist. Prof. Piyarat Buttraporn
Tropical Hygiene	Miss. Siriwan Chanchaen	–	Assist. Prof. Pratap Singhasivanon

Ph.D. (TROP. MED.) (Continued)

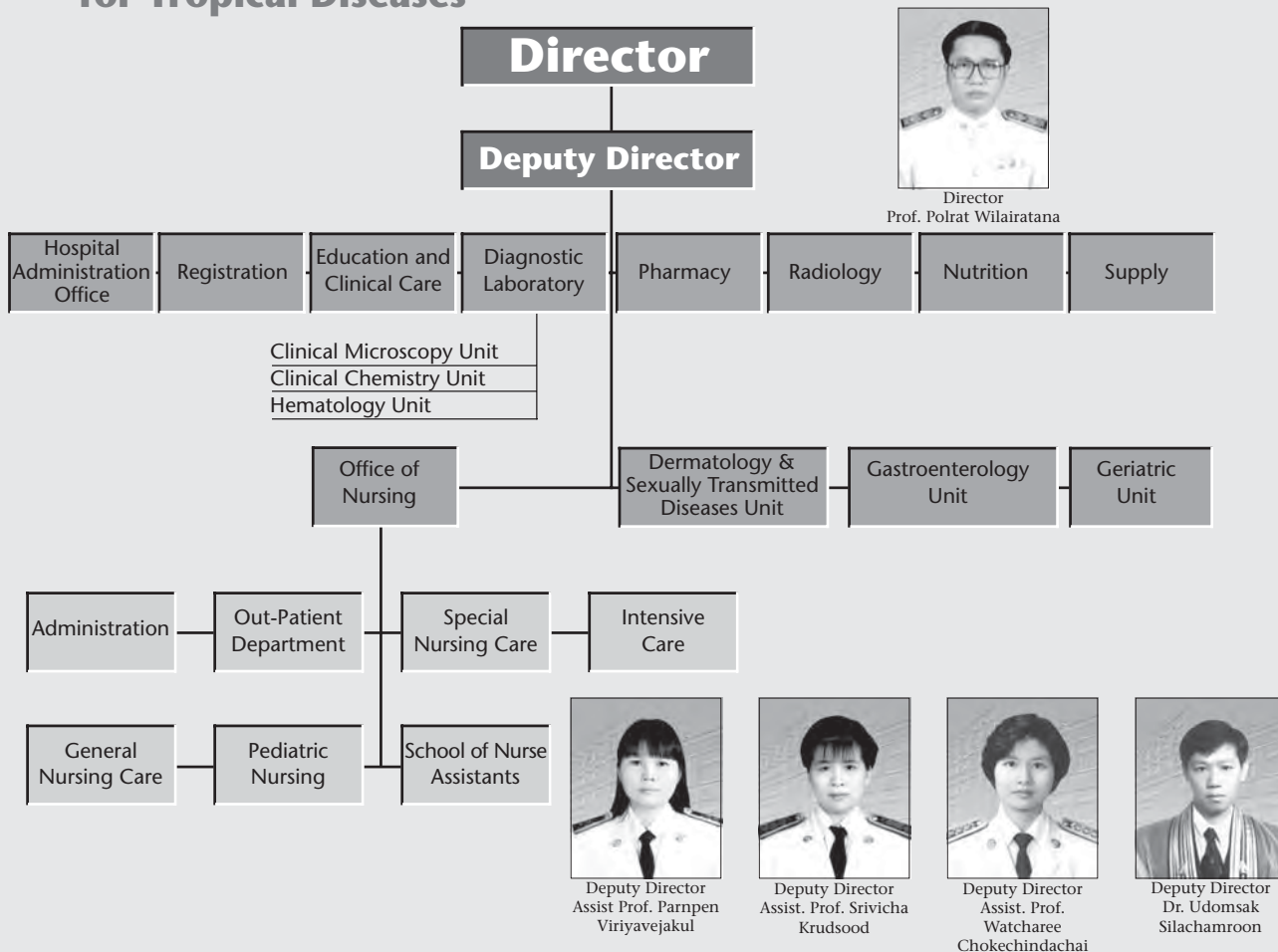
Department	Name	Title of Thesis	Advisor
Tropical Hygiene	Miss Sawanee Tengrungsun	Survival of Thai adult AIDS patients in the tertiary care hospital, Thailand	Assist. Prof. Pratap Singhasivanon
Tropical Nutrition and Food Science	Mrs. Kanjana Hongtong	Platelet fatty acids and serum lipoprotein A in hyperlipid anemia and related heart disease patients and healthy individuals	Assoc. Prof. Supranee Changbumrung
Tropical Nutrition and Food Science	Miss Wanida Pongtaporn	Lipid peroxidant and antioxidant enzymes in smokers before and after vitamin C and E supplement	Assoc. Prof. Rungsun Tungtrongchitr
Tropical Nutrition and Food Science	Miss Pittayaporn Mounnoi	–	Assoc. Prof. Supranee Changbumrung
Tropical Radioisotopes	Mr. Mana Vatakul	Cerebral blood flow in cerebral malaria using SPECT and MR spectroscopy	Prof. Polrat Wilairatana

THE HOSPITAL FOR TROPICAL DISEASES

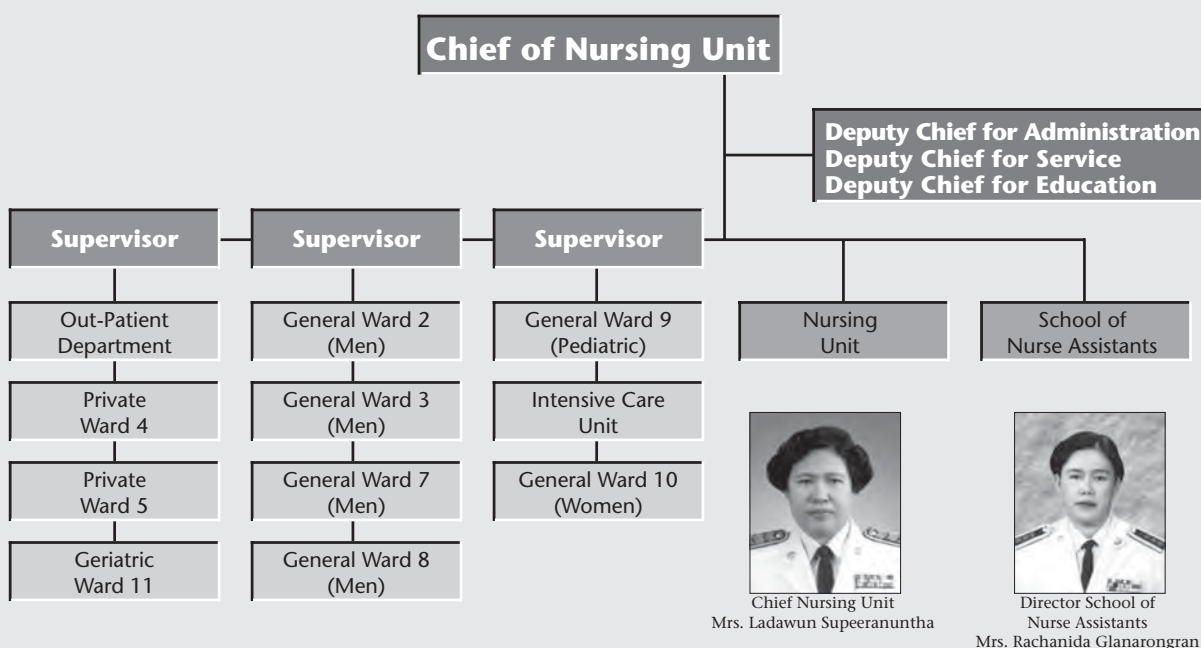
Office Telephone: 2483183 or 2469000-13 ext. 1625, 1625



Organization and Administration of the Hospital for Tropical Diseases



Nursing Unit



MEDICAL CARE SERVICES

Medical care service is one of the main functions of the Faculty of Tropical Medicine. The Hospital for Tropical Diseases, a specialized hospital, provides medical care services for patients suffering from tropical diseases, as well as internal medicine. At present, the Hospital for Tropical Diseases can accommodate up to 250 in-patients. There are services for out-patients, 5 male and female general wards, a children's ward, 2 special care wards, a geriatric ward, an intensive care unit, an intensive care unit for tropical diseases, a gastroenterology division, a dermatology division, and a sexually-transmitted diseases division.

Out-Patient Department services are as follows:

- General medicine: daily except public holidays, 8.00-16.00 hr.
- Malaria clinic: 24 hours daily.
- Electrical stimulation health chair: daily from 6.30-16.00 hr.
- Health examination for emigrant workers: daily except public holidays, 8.00-16.00 hr.
- Laboratory diagnosis for helminthiasis: daily except public holidays, 8.00-10.00 hr.
- Consultation in traveler medicine.
- Center for diagnosis and detection of various specimens in cooperation with other departments and units of the Faculty.
- Medical care services to all Mahidol University students, staff and their families.
- Electrocardiography (ECG).
- Spirometry.
- Audiogram.
- Visual acuity test and color blindness test.

OTHER SPECIAL CLINICS ARE:

- Dermatology clinic: Mondays and Thursdays, 9.00-12.00 hr.
- Sexually-transmitted diseases clinic: Mondays and Thursdays, 9.00-12.00 hr.
- Childrens' clinic: Mondays and Fridays, 13.00-16.00 hr, Wednesdays, 9.00- 16.00 hr.
- Chest clinic: Tuesdays, 9.00-12.00 hr.
- Gastroenterology clinic: Tuesdays, 9.00-12.00 hr.
- Heart clinic: Tuesdays, 9.00-12.00 hr.
- Geriatric clinic: Tuesdays, 9.00-12.00 hr.
- Ear, nose, throat clinic: Tuesdays, 9.00-12.00 hr.
- Gnathostomiasis clinic: Wednesdays and Fridays, 9.00-12.00 hr.



In the fiscal year 1999 (October 1998-September 1999), the numbers of patients treated in the Hospital for Tropical Diseases are classified according to disease as follows:

Diseases	No. of out-patients	No. of in-patients
1. Falciparum malaria	912	900
2. Vivax malaria	913	661
3. Mixed, falciparum and vivax malaria	55	55
4. Malariae malaria	9	8
5. Unidentified infections	269	235
6. Typhoid	9	3
7. Dengue hemorrhagic fever	125	112
8. Hepatitis	170	72
9. Diarrhea	162	30
10. Tapeworm infections	43	-
11. Liver fluke infections	59	-
12. Round worm infections	5	-
13. Whip worm infections	3	-
14. Hookworm infections	18	-
15. Gnathostomiasis	1,262	43
16. Strongyloides infections	30	-
17. Filariasis	8	4
18. Lung infections and other diseases	19,969	1,047
19. Dermal infections	1,723	9

ACTIVITIES DURING THE YEAR:

1. Health check-up for Assistant Nurse students.
2. Health check-up for 733 inhabitants at Bong Tee District, Amphoe Sai Yok, Kanchanaburi Province.
3. 4 health exhibitions on various occasions.
4. Health education on malaria and parasitic infections to college students.
5. Workshop on "Development of media for health education in a hospital".
6. Workshop on "Hospital and health education".
7. Higher education as part of staff development.
8. Visit and training for M.Sc. students from the Faculty of Public Health, Mahidol University, and foreign students.

SPECIAL LABORATORY SERVICES

The Faculty of Tropical Medicine, Mahidol University, offers the following laboratory services and reagents which are not readily available anywhere else.

Immunodiagnoses of various tropical infections

The following table summarizes the diseases/infections for which diagnoses are provided; the serological tests used, the specimen(s) required, the turnaround time for each test, the cost per test and the place where specimens should be sent are included in the table.

Disease/Infection	Serological test used	Specimen required	Time required (hours)	Cost per test (Baht)	Place where specimen should be sent
Gnathostomiasis	1. Indirect ELISA (uses purified specific antigen)	1. 5 ml of clot blood or	3	300 (Thai)	Dept. Microbiology and Immunology via OPD Dept. Helminthology (Western blot only) via OPD
	2. Western blot analysis (uses crude extract of the infective larvae)	2. 1-2 ml of serum	1	2,000 (Foreigner)	
Paragonimiasis	1. Indirect ELISA	1. 5 ml of clot blood or	3	300 (Thai)	Dept. Microbiology and Immunology via OPD
	2. Western blot analysis (partially purified adult worm antigens are used for both assays)	2. 1-2 ml of serum	1	2,000 (Foreigner)	
	3. Both tests (crude extract of adult worms)	3. same	same	same	Dept. Helminthology via OPD
Trichinellosis	1. Indirect ELISA/dot-ELISA	1. 5 ml of clot blood or	3/1	300 (Thai)	Dept. Microbiology and Immunology via OPD
	2. Western blot analysis (the antigen used is either E-S, crude or affinity purified somatic antigens of the infective larvae)	2. 1-2 ml of serum	1	2,000 (Foreigner)	
Strongyloidosis	1. Indirect ELISA/dot-ELISA	1. 5 ml of clot blood or	3/1	300 (Thai)	Dept. Microbiology and Immunology via OPD
	2. Western blot analysis (uses partially purified antigens from filariform larvae)	2. 1-2 ml of serum	1	2,000 (Foreigner)	
	3. Indirect ELISA (crude extract of filariform larvae)	3. same	same	same	Dept. Helminthology via OPD
Toxocariasis	Indirect ELISA (crude extract of adult worms)	same	same	same	Dept. Helminthology via OPD
Leptospirosis	1. Microagglutination method and dark-field microscopy using living leptospire	1. 5 ml of clot blood 2. 1-2 ml of serum 3. Blood absorbed onto filter paper	3	60	Dept. Microbiology and Immunology via OPD or directly to Leptospirosis unit, Dept. Microbiology and Immunology
	2. Antigen detection assay	Urine sample (10 ml)	1	100	
<i>Salmonella</i> septicemia or Salmonellosis and Typhoid	Monoclonal antibody-based dot-blot ELISA using monoclonal antibodies specific to <i>Salmonella</i> core polysaccharide and antigen 9 (antigen detection)	1. Three urine samples collected at 1 hour intervals (5 ml each) 2. Rectal swab, food/water samples in buffered peptone solution	1-2	300	Dept. Microbiology and Immunology via OPD

Disease/ Infection	Serological test used	Specimen required	Time required (hours)	Cost per test (Baht)	Place where specimen should be sent
Cholera caused by serogroup O:1	1. Monoclonal antibody-based dot-blot ELISA using specific monoclonal antibodies to antigen A of <i>V. cholerae</i> serogroup O:1 (antigen detection); diagnostic kits are also available	1. Rectal swab in 1% alkaline peptone solution 2. Watery stool 3. Food sample in 2% alkaline peptone solution 4. Water sample in 10% alkaline peptone solution	1-2	150	Dept. Microbiology and Immunology via OPD
Cholera caused by serogroup O:139	1. Monoclonal antibody-based dot-blot ELISA using specific monoclonal antibodies (antigen detection)	1. Rectal swab in 1% alkaline peptone solution 2. Watery stool	1-3	150	Dept. Microbiology and Immunology via OPD

Other tests

Test for	Test used	Specimen required	Time required (hours)	Cost per test (Baht)	Place where specimen should be sent
Serum folate	Microbiological test using <i>Lactobacillus casei</i>	1. 5 ml of clot blood or 2. 1-2 ml of serum	7	150	Dept. Tropical Radiosotopes
Red cell folate	Microbiological test using <i>Lactobacillus casei</i>	Heparinized blood (2 ml)	7	150	Dept. Tropical Radiosotopes
Vitamin B12	Radiodilution assay	1. 5 ml of clot blood or 2. 1-2 ml of serum	5	150	Dept. Tropical Radiosotopes
Pyrogen free testing	Rabbit test by intravenous injection of the fluid to be tested and determination of body temperatures at intervals	Fluid to be tested	7 days	2,000	Dept. Microbiology and Immunology
Detection of heavy metals in blood (lead, arsenic, cadmium, copper, selenium, chromium, aluminium)	Atomic absorption	1. Heparinized whole blood (1 ml)	2	100	Central Equipment Unit or OPD
Detection of lead in air and waste water	Atomic absorption	1. Air sample 2. Water sample	2	100	Central Equipment Unit
Detection of toluene and xylene in air	Gas chromatography mass spectrophotometer (GCMS)	1. Air sample	2	has not yet been set	Central Equipment Unit

Special reagents available

Reagents available at the Faculty of Tropical Medicine*

Reagent	Quality	Cost	Place where the reagent is available
Monoclonal antibodies to <i>V. cholerae</i> O:1	Monospecificity to antigen A of <i>V. cholerae</i> O:1	150 Baht/ml	Dept. Microbiology and Immunology
Monoclonal antibodies to <i>V. cholerae</i> O:139	Monospecificity to <i>V. cholerae</i> O:139 LPS	150 Baht/ml	Dept. Microbiology and Immunology
Monoclonal antibodies to <i>Salmonella</i> core polysaccharide	Specific to core-polysaccharide of the genus <i>Salmonella</i> (react to all salmonellae)	150 Baht/ml	Dept. Microbiology and Immunology
Monoclonal antibodies to group D <i>Salmonella</i>	Specific to <i>Salmonella</i> antigen 9	150 Baht/ml	Dept. Microbiology and Immunology
Monoclonal antibodies to <i>Pertussis</i> toxin	Specific to S1 component (active, toxic part of pertussis toxin)	150 Baht/ml	Dept. Microbiology and Immunology
Monoclonal antibodies to Verotoxins I and II of enterohemorrhagic <i>Escherichia coli</i>	Specific to A subunit or B subunit	150	Dept. Microbiology and Immunology
Monoclonal antibodies to <i>E. coli</i> O157	Specific to lipopolysaccharide	150	Dept. Microbiology and Immunology
Monoclonal antibodies to the genus <i>Leptospira</i> / pathogenic species <i>interrogans</i>		150	Dept. Microbiology and Immunology
Monoclonal antibodies to E-S antigen of <i>Trichinella spiralis</i>			Dept. Microbiology and Immunology
Polyclonal antibodies specific to <i>V. cholerae</i> O:1 or O:139	Specific to O antigens of serogroup O:1 or O:139, respectively by extensive absorption with heterologous antigens	1,000 Baht/ml	Dept. Microbiology and Immunology
Endotoxin of Gram-negative bacteria (<i>V. cholerae</i> , <i>Salmonella</i> spp., <i>Escherichia coli</i> , and others)	Protein free endotoxin (lipopolysaccharide) from repeated extraction with phenol-water method	500 Baht/mg	Dept. Microbiology and Immunology
Affinity purified <i>-Trichinella spiralis</i> antigen	Highly purified antigen from MAb-based affinity column chromatography	1,000 Baht/mg	Dept. Microbiology and Immunology

* Order should be made in advance

SEAMEO TROPMED REGIONAL CENTRE FOR TROPICAL MEDICINE (TROPMED/Thailand)

FACULTY OF TROPICAL MEDICINE, MAHIDOL UNIVERSITY, BANGKOK, THAILAND

Office Telephone: 2477721; 2469000-13 ext. 1333-1336, 1342, 1345



TROPMED/Thailand Centre
Director and Secretary General/Coordinator
Professor Sornchai Looreesuwan

Deputy Coordinator
Professor Nelia P Salazar

Executive Editor
Southeast Asian Journal of Tropical Medicine and Public Health

Associate Professor Suvanee Supavej

Assistant Coordinator (Programme)
Ms. Vimolsri Panichyanon

Finance Officer
Mrs. Tubtim Potha



Prof. Nelia P Salazar



Assoc. Prof. Suvanee Supavej



Ms. Vimolsri Panichyanon



Mrs. Tubtim Potha



General information on SEAMEO and SEAMEO TROPMED Network

The Southeast Asian Ministers of Education Organization (**SEAMEO**), founded in 1965, is a chartered international organization for the promotion of regional cooperation in education, science, technology and culture.

Member countries are Brunei Darussalam, Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Viet Nam.

Associate Member Countries are Australia, Canada, France, Germany, New Zealand, and the Netherlands.

The Council of Ministers representing the aforementioned countries is called **SEAMEC**. SEAMEO's executory functions are performed by the Secretariat (**SEAMES**) located in Bangkok, Thailand.

SEAMEO TROPMED operates as a Network in Tropical Medicine and Public Health through four **TROPMED Regional Centres** in Indonesia, Malaysia, the Philippines and Thailand, with a coordinating unit, the **TROPMED Central Office** in Bangkok, Thailand.

SEAMEO TROPMED serves to facilitate the strengthening of national and institutional capabilities in research and training through postgraduate academic programmes; workshops, seminars, and technical meetings; multisectoral and multidisciplinary linkages; personnel exchanges; technical consultant services; publications and information dissemination.

The **SEAMEO TROPMED Network** is one of 11 administrative units under SEAMEO, known as **SEAMEO Centres** with specialties in tropical biology (**BIOTROP** in Indonesia); Educational Innovation and Technology (**INNOTECH** in the Philippines); Science and Mathematics (**RECSAM** in Malaysia); Language (**RELC** in Singapore); Higher Education (**RIHED** in Thailand); Regional Training Centre in Viet Nam (**RETRAC**); Open Learning and Distance Education in Indonesia (**SEAMOLEC**); Graduate Study and Research in Agriculture (**SEARCA** in the Philippines); Archeology and Fine Arts (**SPAFA** in Thailand); and Vocational and Technical Education (**VOCTECH** in Brunei Darussalam).

The SEAMEO TROPMED Network and SEAMEO Centres each has a Governing Board consisting of representatives from Member Countries and which is responsible for operational policies, programme quality and evaluation of the unit.

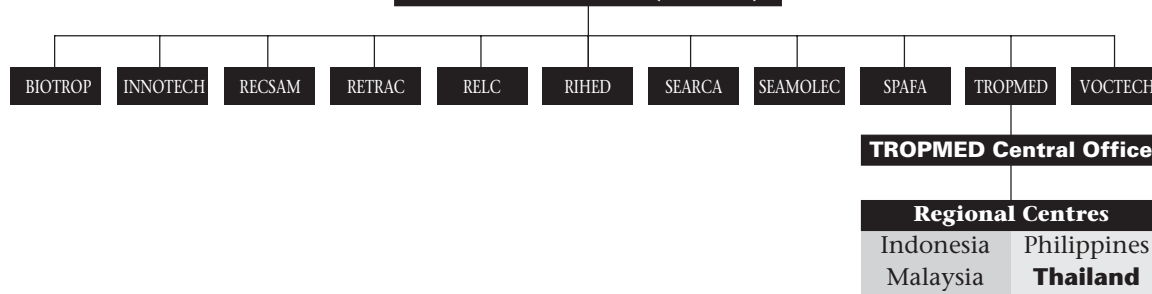
In line with the overall mission of SEAMEO, the primary role of SEAMEO TROPMED is to promote health and to prevent and control disease thereby improving the quality of life of people in South and Southeast Asia.

Southeast Asian Ministers of Education Organization

Member Countries		Associate Members
Brunei Darussalam	Myanmar	Australia
Cambodia	Philippines	Canada
Indonesia	Singapore	France
Lao PDR	Thailand	Germany
Malaysia	Viet Nam	New Zealand
		The Netherlands

SEAMEO Council (SEAMEC)

SEAMEO Secretariat (SEAMES)



Functions of SEAMEO TROPMED Network



- Coordinates regional programmes and activities of the SEAMEO TROPMED Network
- Promotes linkages and networking with national, regional and international organizations and institutions
- Organizes conferences, seminars and training courses in tropical medicine and public health
- Facilitates personnel exchanges between partner institutions
- Undertakes publication of *The Southeast Asian Journal of Tropical Medicine and Public Health* and proceedings of technical meetings and scientific fora
- Manages special projects under various programmes of cooperation in health research and human resources development

SEAMEO TROPMED Regional Centre for Tropical Medicine (TROPMED/Thailand)

TROPMED/Thailand is hosted by the Faculty of Tropical Medicine, Mahidol University under the Ministry of University Affairs Thailand. The Faculty was established in 1960, with specialties in tropical medicine and tropical pediatrics. Courses are conducted at the Bangkok School of Tropical Medicine.

Objectives:

- Teaching about endemic tropical diseases, parasitology, community and preventive medicine, with special reference to Thailand and other countries in Southeast Asia.
- Research in the field and in the laboratory on tropical diseases and public health leading to innovation in alternative control measures of diseases, and promotion of the health of people in Southeast Asia.
- Clinical care of patients suffering from endemic tropical diseases, and clinical research into medical problems of Thailand and neighboring countries, including trials of new chemotherapeutic compounds and new vaccines.



The Annual Report FY 1998/1999 of the SEAMEO TROPED Regional Centre for Tropical Medicine is focused on the following issues :

- I. Accomplishments during FY 1998/1999 according to the 5 Key Result Areas (KRAs)
- II. New initiatives

I. ACCOMPLISHMENTS ACCORDING TO 5 KRAs

KRA 1 : *ENHANCED PROGRAMME QUALITY AND RELEVANCE*

A) *ENHANCED PROGRAMME RELEVANCE*

- 1) **Regular Courses.** In the year under review, there were 110 post-graduate students with 57 new enrollees from 14 countries. Among these, 38 graduated in FY 1998/1999. TROPED/Thailand also offers an undergraduate course leading to the Certificate for Practical Nurse with 87 attendants in FY 1998/1999.

Course	No. of new enrolled students	No. of fee paying students (%)	No. of nationalities	Total no. of students	No. of graduates in FY 1998/99 (%)
DTM&H (6m)	18	13 (70)	10	18	18 (100)
MSc (CTM) (1y)	7	6 (86)	5	7	7 (100)
MSc (TM) (2y)	16	9 (56)	4	45	7 (15)
PhD (CTM) (3y)	1	1 (100)	2	2	- (0)
PhD (TM) (3y)	13	7 (62)	3	38	5 (13)
Cert in Practical Nurse (1y)	87	87 (100)	1	87	87 (100)
Total	142	123 (87)	14	197	124 (63)

- 2) **Joint Degree Programmes.** TROPED/Thailand conducted 3 joint degree programmes with other institutions in Thailand and abroad.

Course	No. of students	No. of fee paying (%)	No. of graduates
DTM ^a	10	10	10
MSc (Clin Epidemiol) ^b	-	-	-
MSc (Trop Pediatr) ^c	1	1	1

- a = Jointly conducted with the Austrian Society of Tropical Medicine and Parasitology.
- b = Joint degree programme of the Faculty of Graduate Studies, Faculty of Public Health and Faculty of Tropical Medicine, Mahidol University.
- c = Joint degree programme of the Faculty of Tropical Medicine, Mahidol University and Liverpool School of Tropical Medicine, UK.

- 3) **Elective Programme in Tropical Medicine.** A one-month elective programme in tropical medicine was organized for 11 medical students from Austria (8) and the United Kingdom (3).
- 4) **Research Attachment Programmes.** Research attachment programmes were arranged for 5 research scientists from France (3), Myanmar (1) and the U.S.A. (1). Eight research articles were published as a result of these programmes.
- 5) **Special Training Programmes.** Special Training Programmes with a duration of 3 weeks to 1 year were individually organized for 8 WHO fellows from Bangladesh (1), Lao PDR (1), the Maldives (1), Nepal (2) and Sri Lanka (3).
- 6) **Seminars/Workshops/Training Courses.** Five regional workshops, 3 training courses and 1 international meeting were organized with a total of 563 participants.
- 7) **Special Lectures/Talks.** Fourteen special lectures/talks were convened with 701 attendants.

B) *ENHANCED PROGRAMME QUALITY*

To be in line with the policy of the Ministry of University Affairs and Mahidol University on quality assurance in education, the Faculty of Tropical Medicine has set up the Committee on Educational Quality Assurance to oversee the enhancement of its programme quality. Quality assurance indicators have been formulated by the Committee to be used for monitoring/evaluating its programme quality.

KRA 2 : *INCREASED ACCESS TO MARKET*

- 2.1 **Marketing Committee.** The Faculty of Tropical Medicine has set up a Marketing Committee comprising 6 members to formulate marketing strategies and the marketing plan of the Centre.
- 2.2 **Marketing Workshop Participation.** Three staff participated in the Marketing Focus Workshop held between 30 November-2 December 1998 in Bangkok, and two Marketing Committee members attended the Marketing Plan Workshop held in Ho Chi Minh City between 8-10 March 1999.
- 2.3 **Active Marketing.** The "Visit TROPMED Day" was organized on 7 January 1999 to allow final year science students to see the facilities and the learning atmosphere of the Faculty of Tropical Medicine. This active marketing approach was very successful, with 193 students and faculty from 6 universities attending.

KRA 3 : *INCREASED LINKAGES*

- 3.1 **More MOU signed.** Three MOU were signed between the Faculty of Tropical Medicine and the following institutions :
- 1) University of Tsukuba, Japan
 - 2) The Health of Animals Laboratory, Canadian Food Inspection Agency, Saskatoon, Canada
 - 3) Liverpool School of Tropical Medicine, Liverpool, UK
- 3.2 **SEAMEO-CIDA Cooperation Programme.** The Faculty of Medicine, University of Calgary, Canada has been as institutional partner of TROPMED/Thailand under the SEAMEO-CIDA Cooperation Programme since 1991. During the year under review, 5 Canadian experts and 3 faculty of TROPMED/Thailand were resource persons of the Workshop on Laboratory Diagnosis of Sexually Transmitted Diseases held at the National Institute of Hygiene and Epidemiology, Vientiane, Lao PDR between 18-29 January 1999. There were 20 participants from Cambodia (5), Lao PDR (9), Viet Nam (5) and one observer from the USA.
- 3.3 **Canadian Intern.** One Canadian intern from Medicine Hat College, Canada has been assigned to TROPMED/Thailand. Her responsibility and other matters concerning the internship are detailed in the status report.
- 3.4 **Consultative Services.** TROPMED/Thailand staff have been invited to give consultative services in projects supported by various agencies.

Projects	Project area	Supporting agency	No. of TROPMED staff invited	Duration
EPH Project in Nepal	Vector borne disease	USAID	4	1 mo
Malaria Control in Indochina	Malaria	EU	1	3 d
Reproductive Health in Viet Nam	Reproductive health	WHO	2	3 wk
Environmental Management in Myanmar	Socio-behavioral	WHO	1	1 wk
Vector Control in India	Vector control	WHO	1	1 wk

- 3.5 **Visitors.** There were 150 visitors from 20 countries in FY 1998/99.

KRA 4 : *IMPROVED FINANCIAL STATUS*

- 4.1 Increase in annual budget from 248.2 million Baht in 1997/98 to 310.0 million Baht in 1998/99. A total 46.6 million Baht was granted for 110 research projects, (18.2 million Baht from international agencies and 28.4 million Baht from Thai Government funding agencies).

KRA 5 : *ENHANCED QUALITY OF SEAMEO MANAGEMENT*

- 5.1 **Number of staff promoted.** Six faculty were promoted (1 Professor, 1 Associate Professor and 4 Assistant Professors); 62 staff were promoted to a higher level and 12 were promoted after gaining higher qualifications.
- 5.2 **Attendance at seminar/workshop/training.** Thirty-eight staff (10%) undertook higher education or study visits in the country or abroad. One hundred and forty four staff (38.8%) attended workshops/seminars/training organized locally or abroad.

5.3 **IT training.** IT training at different levels was provided for 226 staff of the faculty. The training ranged from basic courses to advanced ones.

5.4 **Mini MPA.** 3 staff attended the Mini MPA which was designed for high level administrators.

5.5 **Achievement**

Outstanding staff

4 staff were named Mahidol University outstanding officials.

Publication

109 research results were published in local and international journals.

II. NEW INITIATIVES

1. HASHIMOTO INITIATIVE ON GLOBAL PARASITE CONTROL

Former Prime Minister of Japan, Mr. Hashimoto proposed the initiative on global parasite control at the G8 Summit Meeting in Denver Colorado, U.S.A., in 1997 with the following strategies :

1. Effective international cooperation for the efficient implementation of parasite control;
2. Active pursuit of research that provides a scientific basis for parasite control;
3. Active implementation of effective control projects;
4. Strengthening of the G8 countries' capabilities to deal with parasitic diseases.

The Faculty of Tropical Medicine, Mahidol University has been selected as the Training Centre for Parasite Control for Asia. Preparations are being made for the initiative to come into full operation.

2. SUAN PHUNG FIELD TRAINING CENTRE FOR REGIONAL DEVELOPMENT OF HUMAN RESOURCES IN TROPICAL DISEASE CONTROL

The Faculty of Tropical Medicine has access to land and facilities in Suan Phung District, Ratchaburi Province where a malaria project was carried out. Other facilities are being added.

Suan Phung District has a total area of 2,545 km² consisting of 7 sub-districts with 8,254 households and a population of 33,972. The villagers have relatively low income, and have 5-6 children per family. They suffer from some tropical diseases such as malaria, dengue fever, filariasis, dermatitis, intestinal parasites, iron deficiency anemia and a range of childhood diseases. Detailed mapping of the area to the level of each household was made in the appropriate geographical information system (GIS) as well as demographic, epidemiology and socio-behavioral studies.

This background, together with the willingness of the people to participate in training programmes and to accept researchers/students from other countries into the community, makes this site a particularly suitable one for the proposed training centre.

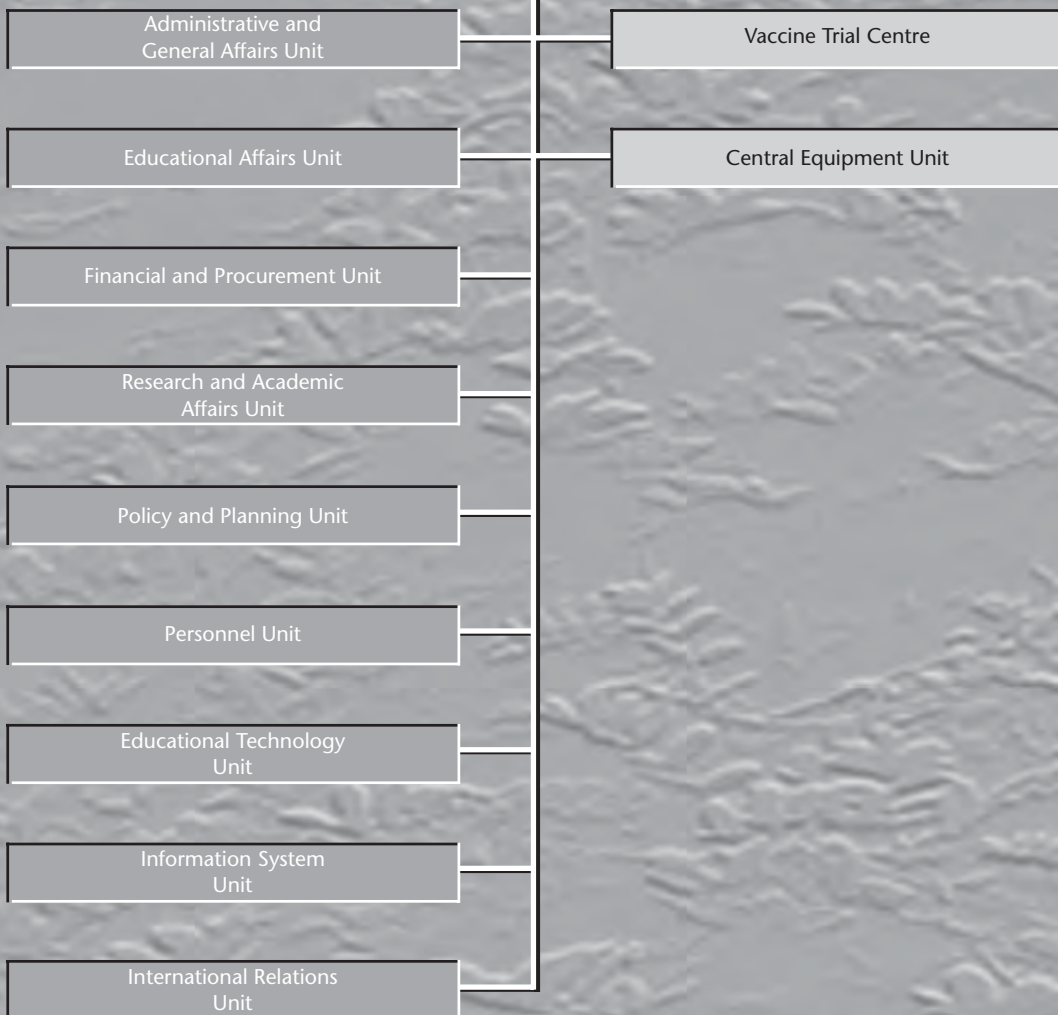


OFFICE OF THE DEAN

Organization and Administration of the Office of the Dean

Office Of The Dean

Secretary Of The Faculty



The Office of the Dean Support Services play an important role in the smooth running of the Faculty and School related activities. These include 10 units as follows:

SECRETARY OF THE FACULTY

Vorapan Singhsilarak B.A.



Vorapan Singhsilarak

ADMINISTRATIVE AND GENERAL AFFAIRS UNIT

Head

Kannikarkaew Pinit B.A. (General Management), B.A. (Business Education)

General Affairs Officer

Aree Masngammuang B.A. (Political Science)

Supavadee Yaowasang B.A. (Lib.Info.Sc.)

Maninthorn Phanumaphorn MBA.

Pranee Kraisor

Public Relations Officer

Thitika Teeranetr B.A. (Communication Arts)



Kannikarkaew Pinit



Aree
Masngammuang



Supavadee
Yaowasang



Thitika Teeranetr



Maninthorn
Phanumaphorn

The Unit is divided into 4 subunits

- 1.1 Documentation
- 1.2 Area and transportation
- 1.3 Public relations and conference organization
- 1.4 Maintenance and repairs

POLICY AND PLANNING UNIT

Head

Yaowapa Pratumsuwan B.A. (Political Science), M.P.A.

Policy and Planning Officer

Thanormsri Ketsuk B.B.A. (Money & Banking)

Jitra Kayee B.B.A. (Money & Banking)

Pramote Ketsuk B.Sc. (Computer Science)



Yaowapa
Pratumsuwan



Thanormsri
Ketsuk



Jitra Kayee



Pramote Ketsuk

The Unit is divided into 3 subunits

1. Coordination and development plan
2. Budget preparation, monitoring, review
3. Management database

PERSONNEL UNIT

Head

Sukanya Ongaree B.A. (Soc. Ant.)

Personnel Officer

Pongsri Konthong

B.A. (General Management)

Nathaporn Kotchasri B.Ed.

Surang Wattanakamolgul

Cert. Marketing

Supaporn Chotivatin Cert. Computer



Sukanya Ongaree



Pongsri Konthong



Nathaporn
Kotchasri



Surang
Wattanakamolgul



Supaporn
Chotivatin

FINANCIAL AND PROCUREMENT UNIT

Somkid Nima

Head

Somkid Nima
B.B.A. (General Management), LL.B.

Accountant Officer

Ketsinee Nima B.B.A. (Accounting)
Prapaiorn Tiacharoen
B.B.A. (General Management)
Chuenboon Aimpraneet
B.A. (General Management)
Tham Chermkhuntod B.B.A. (Accounting)



Ketsinee Nima

Chuenboon
AimpraneetTham
Chermkhuntod

The Unit divided into 3 subunits

1. Finance
2. Accounts
3. Procurement

CENTRAL EQUIPMENT UNIT

Yupa Chantachum

Head

Yupa Chantachum
M.Eng. (Nuclear Tech.)

Scientist

Hathairad Hananantachai
M.Sc. (Environment)

Medical Science Associate

Somchai Poodung
Cert. Medical Science Technology

General Affairs Officer

Tuenjai Ketanon
Dip. Business Administration (Computer, Secretary)



Functions of the Unit

1. To provide scientific instrumentation and laboratory supplies for research and study within the Faculty
2. To offer assistance and guidance in the operation of on-site equipment to the Faculty's staff
3. To provide a general scientific consultancy service for members of the Faculty

EDUCATIONAL AFFAIRS UNIT**Head**

Wanpen Puttitanun B.A.

Educational Affairs Officer

Pramool Sarapantha Ph.D.
Ghosit Chumswat
B.A.(Edn.), M.A.(Hist. & Phil.)

**Scientist**

Chutamas Koomrungruang
B.Sc.(Biology)

Medical Scientist

Wannaporn Ittiprasert B.Sc.(Med. Tech.)

General Affairs Associate

Rangson Praevanit Cert.Commercial
Nutjanat Taiwrob Cert.Commercial
Chiraporn Praevanit Voc.Cert.Commercial
Chutarat Pradabprachr B.Ed.
Aree Buaprae
Nuljun Pochana Cert.Commercial

Staff

Anurat Kalasen Cert.Commercial
Srisuchart Monchonmu Cert.Commercial

Specialist

Paul Adams B.A., Grad. Dip. Lib., M.Mgt.

EDUCATIONAL TECHNOLOGY UNIT

Sompoch Thanuvathana

Head

Sompoch Thanuvathana
Cert. Med. Illus., B.Sc.
(Med. Illus. & A.V. Tech.), M.Ed.(Ed.Tech.)

Illustration Officer

Pluem Kidkian
Dip. Fine Arts, Cert. Med. Illus., B.Sc.
(Med. Illus. & A.V. Tech.)

Saranya Vongngernyuang

B.Sc.(Med. Illus. & A.V. Tech.)

Prastha Kidkian

Bachelor of Fine Art (Painting)

Staff

Tawan Wathanakul Voc. Cert., B.Ed.(Ed.Tech.Inn.)

Kannika Petporee B.A. (General Management)

Sanchai Meeprom



The Unit is comprised of 3 divisions :

1. Audio-Visual Division
2. Museum of Tropical Medicine
3. Computer-Assisted Instruction (CAI) Division

Functions of the Unit

1. To produce and service educational media (such as slides, videos, medical illustrations, multimedia of tropical diseases) for staff of the Faculty and the Hospital for Tropical Diseases, and Assistant Nurses of the Hospital School
2. To prepare and control audio-visual equipment for teaching, seminars and workshops
3. To provide instruction in making educational media to staff and others, both inside and outside the Faculty

INFORMATION TECHNOLOGY UNIT

Duangjai Sahassananda

Head

Duangjai Sahassananda
B.Sc.(Med.Tech.), M.Sc. (Information Technology in Business)

Programmer

Somchai Pichaiyongvongdee
B.Sc.(Public Health), M.Sc. (Technology of Information System Management)

Computer

Kitti thongsri B.Sc. (Computer Science)
Krissada Boonruang B.Sc. (Computer Science)
Wuttichai Kitpremthaworn M.6 (General Affairs Assistant)

General Affairs Associate

Jetsadaporn Chantachorn B.A.(General Management)

Electronic Associate

Pongnatee Kingsawat Dip. in Voc. Ed. (Electronic)

The Information Technology Unit provided information and computer services throughout FY 1998/1999 for the faculty's staff, students and participants in short training courses such as :

I. Lecture

Special lecture in information technology 4 times

II. IT visiting

IT visiting to other institutes 4 times

III. Training

Computer software training 12 times for 266 participants and 36 observers (20 terminals each time)

IV. General services

- | | | |
|---|-------|----------|
| • Computer room | 3,514 | times |
| • UTP installations | 42 | stations |
| • Consulting/Program installation/Virus scan
(Does not include emergency call and telephone consultations) | 392 | times |
| • Computer upgrades | | |
| • Slide making | 4,937 | frames |
| • Laser print | 1,095 | pages |
| • Color print | 379 | pages |
| • Making certificates | 551 | copies |
| • Computer scan image and OCR | 2,768 | pages |

V. Database projects

The unit has 3 projects in information technology:

1. AHEAD project

This project collaborates with the IDRC to make a CD-ROM on Asian Health, Environmental and Allied Databases. The function of the Unit is to collect information on mosquito-borne diseases and prepare it in electronic form.

2. HEED-Net project

This project will collaborate with the Ministry of Public Health; Faculty of Economics, Chulalongkorn University and Faculty of Tropical Medicine, Mahidol University to make health and economic information in GIS form.

*3. SEAMEO-TROPMED (Virtual Library, Homepage).***VI. Application development**

The unit is responsible for development of the computer system and programming in 3 areas:

- Hospital Database Development on a Client/Server Environment; Case study on the Hospital for Tropical Diseases.
- Database development for the service of the Information Technology Unit.
- Stock Database system for the Central Equipment Unit.
- Faculty Homepage on <http://www.mahidol.ac.th/mahidol/tm/h-tromed.htm>
- Intranet for the Administration Section.

INTERNATIONAL RELATIONS UNIT**Head**

Keeratiya Nontabutra B.A.

General Affairs Officer

Wanida Onwan B.A.

Staff

Prachoom Buaprasert



Keeratiya Nontabutra



Wanida Onwan

RESEARCH AND ACADEMIC AFFAIRS UNIT



Pornpimon Adams

Head

Pornpimon Adams
B.Sc.(Biology), M.Sc.(Trop.Med.)

General Affairs Officer

Warissara Chaiyabhandhu
B.A.(General Management)
Sivaporn Sangpan
B.A.(Lib.Info.Sc.)

Illustration Officer

Ronnachai Rarerng
B.Ed.(Ed.Tech.Inn.)
Phaibul Vasanakomut



*Warissara
Chaiyabhandhu*



Sivaporn Sangpan



*Ronnachai
Rarerng*



*Phaibul
Vasanakomut*

The Unit provides publishing facilities such as the Annual Report, the *Mosquito-Borne Diseases Bulletin*, *The Journal of Tropical Medicine and Parasitology*, prospectuses, brochures and other printed materials. The unit also maintains a research and abstract database for the Faculty. Other academic services include distribution of research funding information, and organization of the Faculty's annual Seminar and the Chamlong-Tranakchit Harinasuta Lecture, and secretariat service for the Ethical Committee of Faculty of Tropical Medicine, Mahidol University.

SEMINARS, WORKSHOPS AND TRAINING COURSES AT THE FACULTY OF TROPICAL MEDICINE

between 1 October 1998 - 30 September 1999

1. Joint SEAMEO TROPMED/TDR Small Grants Programme for S.E.Asia

9-13 November 1998

Participants from :

Cambodia	1
Lao PDR	4
Vietnam	1
Total	6

2. The APCO Training Course for Senior Administrators and Leaders of Parasite Control Projects

11-20 November 1998

Participants from :

Bangladesh	2	Bhutan	2
Cambodia	2	Indonesia	2
Lao PDR	2	Nepal	2
Philippines	2	Sri Lanka	2
Thailand	6		
Total		Total	22

3. Consultative Meeting of WHO Experts for Preparation of Practical Guidelines on Management of Snake-bite

29-30 November 1998

Participants from :

India	1	Myanmar	1
Nepal	1	Thailand	2
UK	4		
Total		Total	9

4. Austrian Diploma Course for Tropical Medicine

4-29 January 1999

Participants from :

Austria	14
Total	14

5. Joint International Tropical Medicine Meeting 1999

4-6 August 1999

Participants from :

Australia	3	Austria	8
Belgium	1	Cambodia	1
Canada	2	Egypt	1
France	4	Germany	4
Ghana	1	India	1
Indonesia	5	Israel	1
Japan	6	Lao PDR	5
Malawi	1	Malaysia	2
Myanmar	1	Netherlands	2
Philippines	4	Romania	1
Singapore	4	Sri Lanka	3
Thailand	440	UK	23
USA	3	Vietnam	4
Total		Total	531

6. WHO/SEARO: Workshop on Laboratory Diagnostic Parasitology: A Practical Approach

6-17 September 1999

Participants from :

Cambodia	2	Indonesia	2
Lao PDR	2	Myanmar	2
Philippines	1	Thailand	3
Vietnam	2		
Total		Total	14

7. Training in Laboratory Diagnosis of Parasitic Infections for 1 Cambodian
5-9 October 1998

8. Training in Tropical Medicine for 1 Thai Government Fellow from Romania
14 June-13 December 1999

9. Training in Industrial Toxicants and Pollution Prevention

Venue: Siam City Hotel, Bangkok
Date: Oct 28-30, 1998
Participants: 160

10. Training Workshop in Chemical Risk and Industrial Pollution Prevention

Venue: Hilton International Hotel at Park Nai Lert, Bangkok
Date: May 10-14, 1999
Participants: 30

11. Training Workshop in Industrial Pollution Prevention

Venue: Hilton International Hotel at Park Nai Lert, Bangkok
Date: June 14-15, 1999
Participants: 100

In May, the Faculty hosted two consecutive seminars and demonstrations of high technology transfer in collaboration with French and Thai experts. The first, on "Toxoplasmosis", was held between 13-14 May 1999. International experts participating in this seminar were Prof. Pierre Ambroise-Thomas and Dr Herve Pelloux, of the University of Grenoble, France. The second, on "Deep Mycoses" was held between 17-18 May 1999, with participants including Prof. Grillot, Prof. Ambroise-Thomas, Dr. Pelloux and Prof. Thira, the latter being from Chiang Mai University.

Elective Programme in Tropical Medicine

from 1 October 1998 - 30 September 1999

Name	Country	Institute	Subject	Duration
1. Ms.Sze Yee Yang	Singapore	University of Melbourne	Elective Programme in Tropical Medicine	5 - 29 Jan.1999
2. Ms.Dareen D. Siri	USA	School of Medicine, University of California, San Diego	Elective Programme in Tropical Medicine	3 - 28 May 1999
3. Ms.Farzana Azim Sayani	Canada	Faculty of Medicine, University of Calgary	Elective Programme in Tropical Medicine	21 June - 16 July 1999
4. Mr.Ronik Kanani	Canada	Faculty of Medicine, University of Calgary	Elective Programme in Tropical Medicine	21 June - 16 July 1999
5. Mr.Michio Nagashima	Japan	Asahikawa Medical College	Elective Programme in Tropical Medicine	15 - 22 July 1999
6. Ms.Naho Tsuchiya	Japan	Asahikawa Medical College	Elective Programme in Tropical Medicine	15 - 22 July 1999
7. Mr.Isao Funakoshi	Japan	Asahikawa Medical College	Elective Programme in Tropical Medicine	15 - 22 July 1999
8. Naoki Kishida	Japan	Asahikawa Medical College	Elective Programme in Tropical Medicine	15 - 22 July 1999
9. Ms.Elisabeth Wiendieck	Germany	Friedrich-Schiller-University	Elective Programme in Tropical Medicine	26 July - 31 Aug.1999

Elective Programme in Tropical Medicine (Continue)*from 1 October 1998 - 30 September 1999*

Name	Country	Institute	Subject	Duration
10. Mr.Georg Schaller	Austria	Innsbruck University	Elective Programme in Tropical Medicine	2 - 27 August 99
11. Mr.Gerald Schmidinger	Austria	Innsbruck University	Elective Programme in Tropical Medicine	2 - 27 August 99
12. Ms.Elisabeth Szalay	Austria	Innsbruck University	Elective Programme in Tropical Medicine	2 - 27 August 99
13. Ms.Barbara Kohlweg	Austria	Innsbruck University	Elective Programme in Tropical Medicine	2 - 27 August 99
14. Ms.Tamara Hernler	Austria	Innsbruck University	Elective Programme in Tropical Medicine	2 - 27 August 99
15. Ms.Susanne Scheubmayr	Austria	Innsbruck University	Elective Programme in Tropical Medicine	2 - 27 August 99
16. Ms.Farrah Naz Siddiqui	Pakistan	The Aga Khan University Medical College	Elective Programme in Tropical Medicine	2 - 20 August 99

International Affairs Internship Programme

Name	Country	Institute	Subject	Duration
1. Ms.Saskia I Veltkamp	Canada	Medicine Hat College	International Affairs Internship	14 May - 14 Sept.1999

Research Attachment Programmes*from 1 October 1998 - 30 September 1999*

Name	Country	Institute	Subject	Duration
1. Mr.Daniel P. Mason	USA	Harvard University	Research on Malaria	7 Sept.1998 - Aug.1999
2. Dr.Kabongo Muanza	France	Pitié Salpêtrière	Research on Malaria	9 May - 9 June 1999
3. Dr.Boubacar Traore	France	Pitié Salpêtrière	Research on Malaria	9 May - 9 June 1999
4. Mr.Mathieu Nacher	France	Paris VI University	Research on Malaria	15 June - 15 Oct. 99

INTERNATIONAL LINKAGES

The Faculty of Tropical Medicine has ongoing collaborative activities in research and training with the following :

1. WHO/TDR Programme
2. Freie Universität Berlin, Germany, under the assistance of the German Agency for Technical Cooperation
3. Liverpool School of Tropical Medicine, UK
4. Martsinovskiy Institute of Medical Parasitology and Tropical Medicine, Russian Federation
5. The University of Calgary, Canada
6. Nuffield Department of Medicine, University of Oxford, UK
7. Asian Parasite Control Organization (APCO), Japan
8. The Wellcome Trust, UK
9. International Development Research Centre (IDRC), Canada
10. Japanese Association for Parasite Control (JAPC)
11. SEAMEO TROPMED Regional Centres in Indonesia, the Philippines and Malaysia
12. University of Innsbruck, Austria
13. Queensland Institute of Medical Research, Australia
14. James Cook University of North Queensland, Australia
15. Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ), Germany
16. Department des Maladies Infectieuses et Médecine Tropicale, Groupe Hospitalier Pitié Salpêtrière, France
17. Pasteur Institute, France
18. Chinese Academy of Preventive Medicine, PR China
19. Airlangga University, Surabaya, Indonesia
20. Naval Medical Research Institute, Bethesda, Maryland, USA
21. Agreement for Academic Exchange and Cooperation between University of Tsukuba, Japan and Mahidol University, Kingdom of Thailand
22. Memorandum of Understanding, Collaboration between the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, the SEAMEO TROPMED Network and the Swiss Tropical Institute, Basel, Switzerland
23. Agreement of Co-operation between the Tropical Medicine and Public Health Network of the Southeast Asian Ministers of Education Organization (SEAMEO TROPMED) and the Australian Centre for International and Tropical Health and Nutrition (ACTTHN) of the Queensland Institute of Medical Research and the University of Queensland
24. Memorandum of Understanding between the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand and the Health of Animals Laboratory, Canadian Food Inspection Agency, Government of Canada, Saskatoon, Canada
25. Memorandum of Understanding between the Faculty of Tropical Medicine, Mahidol University and Liverpool School of Tropical Medicine, UK.

The nature of these activities are: collaborative research work; consultative services; personnel, specimen and information exchanges; joint training courses, seminars and conferences.

VISITORS

No.	Name	Country/ Organization
1	Prof. Walther H. Wernsdorfer	Austria
2	Ltc. S.K.B. Hossain	Bangladesh
3	Maj. A.K.M. Abedin	Bangladesh
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5	Dr. Srey Socheath	Cambodia
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8	Mr. Pen Vuthy	Cambodia
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13	Mr. Eric Saifert	Canada
14	Dr. Anand Chandar	Canada
15	Dr. Lai King	Canada
16	Dr. Tom	Canada
17	Dr. Ron Reed	Canada
18	Mrs. Rhonda Gordon	Canada
19	Dr. Frederick Gay	France
20	Dr. Jean Paul Gonzalez	France
21	Dr. Boubacar Traore	France
22	Dr. Kabongo Muanza	France
23	Dr. Peter N. Kessler	Germany
24	Dr. Chusak Prasittisuk	India
25	Dr. Alex Andjaparidze	India
26	Prof. Soedaito	Indonesia
27	Prof. Puruhito	Indonesia
28	Prof. Marishur S. Wiyadi	Indonesia
29	Prof. Rika S. Triyoga	Indonesia
30	Prof. Fukuhara	Japan
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42	Mr. Meiji Kuga	Japan
43	Mr. Hiroshi Uno	Japan
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45	Dr. Shigeyuki Kano	Japan
46	Dr. Takeshi Kasai	Japan
47	Dr. Shin-Ichiro Kawazu	Japan
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49	Dr. Eisaku Kimura	Japan
50	Dr. Masatsugu Kimura	Japan
51	Dr. Fujiro Sendo	Japan
52	Dr. Teruaki Amano	Japan
53	Mr. Naoaki Kuroda	Japan
54	Mr. Sugihara Makoto	Japan
55	Mr. Chih-Kuang Lin	Japan
56	Ms. Satomi Hikichi	Japan
57	Mr. Kiichirou Yoshida	Japan
58	Ms. Takano Makiko	Japan
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65	Ms. Akiko Yamada	Japan
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67	Mr. Tomonori Aoyama	Japan
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69	Mr. Satoshi Ichihara	Japan
70	Mr. Takasuke Ogawa	Japan
71	Mr. Naoya Haibara	Japan
72	Ms. Eri Suda	Japan
73	Ms. Miyuki Tutui	Japan

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75	Ms. Eri Arai	Japan
76	Ms. Naomi Yoshikawa	Japan
77	Ms. Tomoko Tani	Japan
78	Capt. Ken-ichi Hirayama	Japan
79	Dr. Hiroshi Omae	Japan
80	Dr. Nobuhiko Nagai	Japan
81	Dr. Yutaro Kaneko	Japan
82	Dr. Manivanh Southammavong	Lao PDR
83	Dr. Outhone Anothay	Lao PDR
84	Dr. Rommany Pholsena	Lao PDR
85	Dr. Vanphanom Sychareun	Lao PDR
86	Dr. Alongkone Phengsavanh	Lao PDR
87	Dr. Bunchan Keomanivong	Lao PDR
88	Dr. Keomanivanh Khammanivong	Lao PDR
89	Dr. Bounthaphany Bounxouei	Lao PDR
90	Dr. Mayboun Heuangvongsi	Lao PDR
91	Dr. Sonxay Phanyanouvong	Lao PDR
92	Dr. Mauro Valencia-Juillerat	Mexico
93	Dr. D.J. Gubler	WHO/SEARO Experts on DF/DHF
94	Dr. Linda S. Lloyd	WHO/SEARO Experts on DF/DHF
95	Dr. Suchitra Nimmannitya	WHO/SEARO Experts on DF/DHF
96	Dr. Viroj Tangcharoensathien	WHO/SEARO Experts on DF/DHF
97	Dr. Wiwat Rojanapithayakorn	WHO/SEARO Experts on DF/DHF
98	Dr. Pinan Daenggharn	WHO/SEARO Experts on DF/DHF
99	Dr. Seeviga Saengtharatip	WHO/SEARO Experts on DF/DHF
100	Mr. Shen Erli	PR China
101	Mr. Gong Xinsheng	PR China
102	Mr. Zhang Wei	PR China
103	Mr. Dong Xingqi	PR China
104	Dr. Michael Nathan	Switzerland
105	Dr. Paul Garner	UK
106	Prof. David H. Molyneux	UK
107	Maj. Duane R. Hospenthal	USA
108	Maj. Peter J. Weina	USA
109	Dr. Pandu Wijeyaratne	USA
110	Dr. Margaret Calloway	USA
111	Ms. Betty Carvellas	USA
112	Mr. Richard E. Jacobstein	USA
113	Mrs. Sheila P. Jacobstein	USA
114	Mrs. Helen A. Sidel	USA
115	Dr. Leo J. Sidel	USA
116	Ms. Karen A. Tucker	USA
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118	Mrs. Alice A. Kagl	USA
119	Mrs. Lana L Hays	USA
120	Laurie Elizabeth Emert	USA
121	Kristen Adele Copeland	USA
122	Lorrie Lynne Henson	USA
123	Roopal Desai	USA
124	Assoc.Prof. Danuta Kozbor	USA
125	Dr. Tran Thi Lua	Vietnam
126	Dr. Vu Song Te	Vietnam
127	Mrs. Truong Thi Ro	Vietnam
128	Mr. Nguyen Van Dong	Vietnam
129	Mr. Nguyen Van Quyet	Vietnam
130	Mr. Nguyen Van Luu	Vietnam
131	Mr. Nguyen Quang Hoanh	Vietnam
132	Mr. Doung Cong Lieu	Vietnam
133	Dr. Bui Van Dinh	Vietnam
134	Prof. Truong Dinh Kiet	Vietnam
135	Dr. Pham Hung Luc	Vietnam
136	Dr. Nguyen Trong Thong	Vietnam
137	Dr. Pham Van Linh	Vietnam

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Chantima Lohachit	tmclh@mahidol.ac.th	Medical and freshwater malacology Limnology/Ecology/Spermatogenesis (TEM) Environmental Health
Chotechuang Panasoponkul	tmcpn@mahidol.ac.th	Vector borne diseases eg. filariasis, malaria and field work
Chukiat Sirivichayakul	tmcsw@mahidol.ac.th	General pediatrics Chemotherapy of childhood malaria Parasitic infection in children Childhood diarrhea
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Lecturers	E-mail Address	Field of Specialization/expertise
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Somjai Leemingsawat	tmslm@mahidol.ac.th	Medical entomology/Tick and mite-borne diseases/Filarial parasites and vectors
Songsak Petmitr	tmspm@mahidol.ac.th	Molecular biology/Cancer
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Srisin Khusmith	tmskm@mahidol.ac.th	Immunology/Molecular biology/Malaria

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Wanchai Phatihatakorn	tmwpk@mahidol.ac.th	Environmental health impact assessment GRD Monitoring, evaluate and surveillance of parasitic diseases
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Waranya Wongwit	tmwwg@mahidol.ac.th	Biochemistry of parasites (gene therapy)
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Yuvadee Mahakunkijcharoen	tmymh@mahidol.ac.th	Immunology of parasitic infections and bacterial infections

ONGOING RESEARCH PROJECTS OF THE FACULTY OF TROPICAL MEDICINE IN 1999

No.	Ongoing Research Projects in 1999	Grants	Principal Investigator
Department of Clinical Tropical Medicine			
1	Emergencies of liver fluke infections during dry season: Lam-Takong and Mae-Kwuang National Reservoirs		Prof. Swangjai Pungpak
2	Combination of artesunate and mefloquine in acute uncomplicated falciparum malaria	Tropical Diseases Trust	Assoc. Prof. Yupaporn Wattanagoon
3	Comparative assessment of <i>in vivo</i> and <i>in vitro</i> sensitivity of <i>Plasmodium vivax</i> to chloroquine		Assoc. Prof. Kesara Na Bangchang
4	Investigation of the response of <i>Plasmodium falciparum</i> to a combination regimen of artesunate plus mefloquine in Mae Sot District, Tak Province		Assoc. Prof. Kesara Na Bangchang
5	Study on partition of an antimalarial mefloquine		Assoc. Prof. Kesara Na Bangchang
6	Bioavailability and bioequivalency of suppositories larval artesunate and artemether in healthy volunteers		Assoc. Prof. Kesara Na Bangchang
7	Host factors related to severe and complicated falciparum malaria	JSPS and NRCT	Prof. Sornchai Looreesuwan
8	A phase II/III clinical trial of oral dihydroartemisinin (Twisinin®) for treatment of uncomplicated <i>Plasmodium falciparum</i> malaria in Thailand	T-2	Prof. Sornchai Looreesuwan
9	Relationship of <i>Plasmodium</i> antigen and antibody profiles to therapeutic response in falciparum malaria	SEAMEO-TROPED Network and Wellcome Unit of Great Britain	Prof. Sasithon Pukrittayakamee
10	PCR-RFLP detection of <i>Plasmodium vivax</i> DHDFR mutations	The Thailand Research Fund (TRF)	Prof. Sasithon Pukrittayakamee
11	Treatment and control of important tropical diseases together with dental health and social science in people living in Saiyok, Kanchanaburi Province	Mahidol University	Prof. Polrat Wilairatana
Department of Helminthology			
12	The IFAT for human gnathostomiasis	Mahidol University	Miss Wattana Pahuchon
13	Monoclonal antibody-based competitive ELISA and indirect ELISA for immunodiagnosis of trichinosis	Mahidol University	Mrs. Supaporn Nuamtanong
14	Comparison of biochemical extract preparations of <i>Cysticercus cellulosae</i> by SDS-polyacrylamide gel electrophoresis and immunoblot technique	Mahidol University	Assist. Prof. Paron Dekumyoy
15	Experimental infection of freshwater fish in Thailand with infective stage of <i>Angiostrongylus</i>	Mahidol University	Assist. Prof. Chalit Komalamisra
16	<i>Toxocara canis</i> larval antigens for serodiagnosis of human toxocariasis	Mahidol University	Assist. Prof. Wanna Maipanich
17	Efficacy of high dose mebendazole against trichuriasis in adult patients	APCO, Japan	Assoc. Prof. Jitra Waikagul
18	The effects of <i>Trichinella spiralis</i> infection on renal functions in rat	Mahidol University	Mr. Panyawut Hiranyachattada
19	Comparative studies on surface ultrastructure of adult worm of <i>Paragonimus</i> sp. in Thailand	Mahidol University	Assist. Prof. Sanan Yaemput
20	Seasonal variation in the intensity of <i>Gnathostoma</i> larvae in eels in Nakhon Nayok Province	Mahidol University	Assist. Prof. Wichit Rojekkittikhun

No.	Ongoing Research Projects in 1999	Grants	Principal Investigator
Department of Helminthology (Continued)			
21	Studies on the efficacy of Thai traditional herbal medicines in the treatment of opisthorchiasis in hamsters		Mr. Panyawut Hiranyachattada
22	Species determination of human hookworm in school children in Nakhon Sri Thammarat Province	APCO, Japan	Assoc. Prof. Malinee Thairungroj
Department of Medical Entomology			
23	Evaluation of certain chemical stimuli as attractants for sound trapping of <i>Culex tritaeniorhynchus</i>	Faculty of Tropical Medicine	Assoc. Prof. Vanida Deesin
24	Combination effects of <i>Bacillus sphaericus</i> 2362 and the insect growth regulator for the control of anopheline vector in small scale field trial	Faculty of Tropical Medicine	Assoc. Prof. Yupha Rongsriyam
25	Critical biology and disease transmission indices in dengue	Faculty of Tropical Medicine	Assoc. Prof. Yupha Rongsriyam
26	Comparative susceptibility to oral infection with dengue virus among local strain of <i>Aedes aegypti</i> collected at different seasons of the year	The National Research Council of Thailand	Assist. Prof. Supatra Thongrungrat
27	Computer aided management and service of the biological museum, Faculty of Tropical Medicine	NECTEC	Assoc. Prof. Chamnarn Apiwathnasorn
28	Contamination and accumulation of some heavy metals, lead and cadmium in <i>Culex quinquefasciatus</i> and <i>Musca domestica</i>	Mahidol University	Assoc. Prof. Chamnarn Apiwathnasorn
29	Specificity of the synthetic primers from sequencing DNA fragments of <i>Anopheles minimus</i>	Faculty of Tropical Medicine	Assist. Prof. Narumon Komalamisra
30	Impacts of permethrin impregnated bednets on <i>Anopheles dirus</i>	The National Research Council of Thailand	Assoc. Prof. Vanida Deesin
31	<i>Artemisia annua</i> oil as a repellent against mosquito vectors in Thailand	Mahidol University	Mrs. Kaewmala Palakul
Department of Microbiology and Immunology			
32	Anaerobic bacteria intraabdominal infection	Mahidol University	Assoc. Prof. Suvanee Supavej
33	Production of monoclonal antibodies for use in the diagnosis of scrub typhus	Faculty of Tropical Medicine	Assist. Prof. Varee Wongchotigul
34	Production of monoclonal antibodies against cyst specific antigens of <i>Entamoeba histolytica</i>	Faculty of Tropical Medicine and The National Research Council of Thailand	Assoc. Prof. Nitaya Thammapalerd
35	Detection of dengue virus in mosquitoes (<i>Aedes aegypti</i>) by polymerase chain reaction compare with virus-cultivation	Mahidol University	Assoc. Prof. Wipawee Usawattanakul
36	Development of polymerase chain reaction for the diagnosis of vivax malaria	Mahidol University	Assoc. Prof. Pramuan Tapchaisri
37	Identification and characterization of T cell epitopes on <i>P. falciparum</i> sporozoite surface protein 2 recognized by human	Naval Medical Research Institute	Prof. Srisin Khusmith
38	The use of recombinant <i>Entamoeba histolytica</i> pyruvate: ferredoxin oxidoreductase (r PFOR) as a candidate vaccine against invasive amebiasis		Assoc. Prof. Nitaya Thammapalerd
39	Production of recombinant pyruvate: ferredoxin oxidoreductase of <i>Entamoeba histolytica</i> (Eh rPFOR) and its application for diagnosis of invasive amebiasis		Assoc. Prof. Nitaya Thammapalerd

No.	Ongoing Research Projects in 1999	Grants	Principal Investigator
Department of Microbiology and Immunology (Continued)			
40	Development of leptospirosis diagnosis	NSTDA	Prof. Wanpen Chaicumpa
41	Pathology of enterohemorrhagic <i>Escherichia coli</i> infection	The Thailand Research Fund and University of Tsukuba, Japan	Prof. Wanpen Chaicumpa
42	Development of schistosomiasis diagnosis	NSTDA	Prof. Wanpen Chaicumpa
43	Development of an antigen detection assay for diagnosis of leptospirosis	BIOTEC	Prof. Wanpen Chaicumpa
44	Rapid detection of <i>Salmonella</i> in contaminated foods by immunomagnetic enrichment and enzyme immunoassay	The Thailand Research Fund	Assist. Prof. Yuvadee Mahakunkijcharoen
45	Pathology of enterohaemorrhagic <i>E. coli</i> and the protective role of antibody	TRE, NSTDA and University of Tsukuba, Japan	Prof. Wanpen Chaicumpa
46	Schistosomiasis mekongi: diagnosis and innate immunity	Faculty of Tropical Medicine and NSTDA	Prof. Wanpen Chaicumpa
47	Rapid diagnosis of salmonellosis using dip stick method	Mahidol University	Prof. Wanpen Chaicumpa
48	Development of opisthorchiasis by immunological method	Ministry of Public Health and Faculty of Tropical Medicine	Prof. Wanpen Chaicumpa
49	Diagnosis of trichinellosis using affinity purified antigen	Faculty of Tropical Medicine, NSTDA and University of Tsukuba, Japan	Prof. Wanpen Chaicumpa
50	Production of monoclonal antibodies to <i>Bordetella pertussis</i> filamentous haemagglutinin	Faculty of Tropical Medicine, NSTDA and University of Tsukuba, Japan	Assoc. Prof. Manas Chongsa-nguan
51	Antigenic analysis of <i>V. cholerae</i> isolated in Thailand for epidemic tracing	University of Tsukuba, Japan	Assoc. Prof. Pramuan Tapchaisri
52	Production of specific monoclonal antibodies to <i>Toxoplasma gondii</i>	NSTDA and University of Tsukuba, Japan	Prof. Wanpen Chaicumpa
53	Studies on allergenic components of <i>Dermatophagoides pteronyssinus</i>	NSTDA	Prof. Wanpen Chaicumpa
54	Studies on allergic components of cockroaches (<i>Blatta orientales</i>)	NSTDA	Prof. Wanpen Chaicumpa
55	Diagnosis of gnathostomiasis using specifically purified antigen	NSTDA	Prof. Wanpen Chaicumpa
56	Comparison between R-PE and phycoerythrin-labeled MAb probes for the detection of <i>E. histolytica</i> in faecal materials		Assoc. Prof. Nitaya Thammaphalerd
Department of Protozoology			
57	Isolation and characterization of DNA topoisomerase II from <i>Trichomonas vaginalis</i>	The National Research Council of Thailand	Assist. Prof. Porntip Petmitr
58	Prevalence of <i>Toxoplasma gondii</i> in Thai healthy population		Assist. Prof. Yaowalark Sukthana
59	Serological study of <i>Toxoplasma gondii</i> antibody in kidney recipients	Thanad-Molee Choman Foundation	Assist. Prof. Yaowalark Sukthana
60	Comparison of <i>Toxoplasma gondii</i> antibody detection between in-house latex agglutination and commercial test	Thanad-Molee Choman Foundation	Assist. Prof. Varaporn Suphadtanapongs

No.	Ongoing Research Projects in 1999	Grants	Principal Investigator
Department of Protozoology (Continued)			
61	Isolation and characterization of DNA helicase from <i>Plasmodium falciparum</i>	Thailand Research Fund	Assist. Prof. Porntip Petmitr
62	Comparison study of <i>Toxoplasma gondii</i> antibody by using latex agglutination and Dye test	Bio Merieux Co., Ltd.	Assist. Prof. Yaowalark Sukthana
63	Study of <i>Toxoplasma gondii</i> antibody in the population of provinces with a high risk of HIV	Mahidol University	Assist. Prof. Yaowalark Sukthana
Department of Social and Environmental Medicine			
64	Early detection of rifampicin resistant <i>M. leprae</i> among Thai leprosy patients	The National Research Council of Thailand	Dr. Pongrama Ramasoota
65	Opisthorchiasis risk foods assessment	The National Council of Women of Thailand	Assist. Prof. Wanchai Phatihatakorn
66	Hazardous substance management and development of a computerized database inventory of major hazardous substances used at the Faculty of Tropical Medicine, Mahidol University	Mahidol University	Assist. Prof. Voranuch Wangsuphachart
67	Search for a model to prevent alcohol consumption among Thai students	Mahidol University	Mr. Rungwit Mas-ngammueng
68	Hazardous waste in industries	Mahidol University	Assist. Prof. Ladda Tangbanluekal
*69	Effect of insecticide on the female reproductive system	Tokyo University	Prof. Ryutaro
70	Control of soil-transmitted helminths in primary school in Southern Thailand	Mahidol University	Mr. Prasart Vorasant
*71	Air pollution mitigation from the industrial sector	Department of Industrial Works, Ministry of Industry	Dr. Sangsan Panich
Department of Tropical Hygiene			
72	Epidemiological study of nutritional deficiency among Karen preschool children	Faculty of Tropical Medicine	Mr. Surapon Yimsamran
73	Malaria in Thai-Burmese border: interaction between host, agent, and environment	Government Budget	Assist. Prof. Pratap Singhasivanon
74	Assessment of risk factors of mortality associated with vehicular crashes in a central province of Thailand: before and after enforcement of safety service law	SEAMEO-GTZ [M.Sc. Epidemiology (Public Health) Project]	Dr. Nilarat Premmanisakul
Department of Tropical Nutrition and Food Science			
75	Identification of gene mutation in lung cancer cells in Thai patients	Mahidol University China Medical Board	Assist. Prof. Songsak Petmitr
76	Food and health relationship in Asian population	Palm oil Research Institute of Malaysia	Assoc. Prof. Supranee Changbumrung
77	Molecular biology of carcinogenesis in lung cancer	The Thailand Research Fund	Assist. Prof. Songsak Petmitr
78	Development of food and medicinal plants	Government Budget	Assoc. Prof. Supranee Changbumrung
79	Serum leptin concentration in obese subjects	Free University, Berlin, Germany	Assoc. Prof. Rungsunn Tungtrongchitr
80	Micronutrients and oxidative stress in obese subjects	Free University, Berlin, Germany	Assoc. Prof. Rungsunn Tungtrongchitr
81	The effects of smoking on work performance in relation to the phenotype of alpha-1-antitrypsin	Institute of Tobacco Consumption Control Medical Service, Ministry of Public Health	Prof. Praneet Pongpaew

No.	Ongoing Research Projects in 1999	Grants	Principal Investigator
Department of Tropical Pathology			
82	Pathogenic effect of nitric oxide in sera and cerebrospinal fluid on cerebral malaria	Thailand Research Fund and Mahidol University	Assist. Prof. Yaowapa Maneerat
83	Liver pathology in AIDS	Ministry of University Affairs	Assist. Prof. Parnpen Viriyavejakul
84	Study of opportunistic infections in AIDS by needle biopsy	Mahidol University	Assist. Prof. Parnpen Viriyavejakul
85	Immunohistochemistry study of infectious diseases in liver necropsy of AIDS	WHO	Assist. Prof. Parnpen Viriyavejakul
86	Nitric oxide production by <i>Plasmodium falciparum</i> stimulated endothelial cell	Mahidol University	Assist. Prof. Yaowapa Maneerat
Department of Tropical Pediatrics			
87	A phase IV, observer-blind, randomized, controlled, trial to evaluate safety, tolerability and immunogenicity of the Chiron acellular pertussis vaccine combined with diphtheria and tetanus toxoids (DTwP), when administered to healthy Thai infants at 2, 4 and 6 months of age		Prof. Arunee Subchareon
88	Safety and immunogenicity of tetravalent dengue vaccine formulations in Thai adult volunteers (DEN 04198)	Pasteur Mérieux Serum and Vaccines, Lyon, France	Assoc. Prof. Pornthep Chanthavanich
89	Clinical efficacy and pharmacokinetics of suppositoried artesunate combined with mefloquine in the treatment of severe childhood falciparum malaria		Assoc. Prof. Krisana Pengsaa
90	A multicentric, randomized, double blind, placebo-controlled, parallel group study to assess the efficacy, safety and tolerability of acetorphan (Tiorfan™) 1.5 mg/kg body weight tid pa plus oral rehydration therapy in the treatment of acute diarrhea in children	Smith Kline Beecham Pharmaceuticals Co., Ltd.	Assoc. Prof. Pornthep Chanthavanich
91	Clinical efficacy and pharmacokinetics of suppositoried artesunate combined with mefloquine in the treatment of uncomplicated childhood falciparum malaria		Assist. Prof. Chukiat Sirivichayakul
92	A prospective evaluation of severe dengue assay	Kit tests from Pun Bio Pty. Co., Ltd. Brisbane, Australia and Integrated Diagnostics., Baltimore, USA.	Assist. Prof. Watcharee Chokejindachai
93	The relationship of mixed infection and severity of falciparum malaria		Assist. Prof. Watcharee Chokejindachai
94	Influenza: incidence and clinical manifestations in nurse assistant students of the Faculty of Tropical Medicine, Mahidol University, Thailand	Pasteur Mérieux Connaught, Thailand	Assist. Prof. Chukiat Sirivichayakul
Department of Tropical Radioisotopes			
95	Study of four Thai medicinal herbs as individual and combinations for anti-snake venoms		Assist. Prof. Channarong Sanghirun
96	Viscosity of red cell ghosts and hemoglobin of red cells from patients with <i>Plasmodium falciparum</i> malaria	Mahidol University	Assist. Prof. Petcharin Yamarat

No.	Ongoing Research Projects in 1999	Grants	Principal Investigator
Department of Tropical Radioisotopes (Continued)			
97	Effect of garlic on blood rheology and prevention of thrombolism	The National Research Council of Thailand	Assist. Prof. Petcharin Yamarat
Vaccine Trial Centre			
98	Development of new vaccines against cholera due to <i>Vibrio cholerae</i> O139	WHO	Assoc. Prof. Punnee Pitisuttithum
99	A phase I/II, double-blind, placebo-controlled study of the Chiron biocine HIV Thai E gp 120/MF59 vaccine administered alone or combined with the Chiron biocine HIV SF2 gp120 antigen in healthy HIV-seronegative Thai adults	WRAIR, USA	Assoc. Prof. Punnee Pitisuttithum
100	A phase I/II trial to evaluate the safety and immunogenicity of AIDSVAX™ B/E vaccine in Bangkok, Thailand	VAXGEN Co, Ltd.	Assoc. Prof. Punnee Pitisuttithum
101	A multicenter, randomized, double-blind, phase II study to evaluate the safety, tolerance and efficacy of multiple doses of SCH 56592 versus fluconazole in the treatment of oropharyngeal candidiasis (OPC) in HIV-positive patients	Schering Plough Research Institute	Assoc. Prof. Punnee Pitisuttithum
102	Phase I/II trial of Pasteur Merieux Connaught live recombinant ALVAC-HIV (vCP 1501) Priming with Vaxgen GP 120 B/E (AIDSVAX™ B/E) Boost in Thai HIV-Seronegative adults	Walter Reed Army Institute of Research	Assoc. Prof. Punnee Pitisuttithum
*103	A phase III trial to determine the efficacy of AIDSVAX™ B/E Vaccine in intravenous drug users in Bangkok, Thailand	VAXGEN Co., Ltd.	Bangkok AIDS Vaccine Evaluation Group

* Faculty of Tropical Medicine Staff are Co-investigators.

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