TWENTY YEARS OF THE WELLCOME-MAHIDOL UNIVERSITY, OXFORD TROPICAL MEDICINE RESEARCH PROGRAM

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This year the Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme celebrates its twentieth anniversary. This is a Wellcome Trust supported tropical medicine research collaboration between the Faculty of Tropical Medicine, Mahidol University and the Nuffield Department of Clinical Medicine, University of Oxford. The Wellcome Trust is a completely independent charity with a long tradition of supporting tropical medicine research which originates from the will of Sir Henry Wellcome. We are part of this tradition. Sir Henry was a great entrepreneur, collector, and philanthropist, and when he died he left his estate to a Trust whose job was to support "medical research for the good of mankind", and within this he identified, specifically, tropical medicine. I have been requested to write a personal review of the history of our unit. It cannot do justice to all those who have contributed so much to the research work over the past two decades, but I hope it is a fair reflection of events.

In the late 1970s, the Wellcome Trust became interested in setting up and supporting a tropical medicine research unit in Asia. Professor (now Sir) David Weatherall (Nuffield Professor of Medicine, University of Oxford), Dr Peter Williams (Director of the Wellcome Trust), and Dr (now Professor) David Warrell visited jointly several countries in search of a site for such a unit. They were impressed and enthused by the research opportunities, and charmed by the kind welcome given to them here in Thailand by Professors Chamlong and Khunying Tranakchit Harinasuta at the Faculty of Tropical Medicine, Mahidol University. The original introduction had been made through Professor Herbert Gilles of the Liverpool School of Tropical Medicine, where both Professor Chamlong and Professor Khunying Tranakchit had completed their postgraduate studies. A research collaboration was agreed upon and a memorandum of understanding was signed, and soon afterwards David (a physician) and his wife Mary (a clinical virologist) left Oxford for Bangkok. The Faculty kindly provided an office and laboratory above the hospital outpatients department. Khun Patchari Prakongpan was recruited as the administrator, and she has remained at the helm ever since.

The unit planned to work specifically on three areas of research - malaria, rabies, and snake bite. Arrangements were soon made to start clinical research work on severe malaria in Pra Pokklao Hospital, Chantaburi. Dr Sornchai Looareesuwan (now Professor and Dean of the Faculty of Tropical Medicine) joined David and Mary, and all three set off in May 1979 to conduct a double-blind placebo-controlled study of dexamethasone in cerebral malaria. This famous study has since become a benchmark for clinical trials in severe malaria. In September 1979 I arrived from Oxford and, after some language tuition, joined the team in Chantaburi. In those days Chantaburi was reached by a laterite track from Klaeng (now there is a dual carriage motorway). Indeed when the then hospital director (Dr Chaisit Dharakul) took up his post, he had to go to Chanthaburi by sea as there was no road! ! We found ourselves in the middle of an epidemic of cerebral malaria as an influx of non-immune people from the North East (Isan) came to pick fruit or dig for gems in the malarious hills around Chantaburi. We admitted up to four cases of cerebral malaria each day to the intensive care unit, and, in between, saw cases of snake bite (mainly in workers from the fruit orchards who had disturbed a Malayan Pit Viper). The following year we returned to Chantaburi twice, and work began in Bangkok on rabies. We concentrated initially on a detailed clinical documentation of severe malaria in the course of specific studies on pathophysiology and antimalarial treatment. At that time, only twenty years ago, there was very little convincing information on the pathophysiological basis for vital organ dysfunction in malaria, and antimalarial treatment regimens for severe malaria were still largely empirical. Quinine had replaced chloroquine many years previously in Thailand but there was confusion over the correct dose. Some international authorities suggested that the dose of parenteral quinine in severe malaria should be as low as 5mg/kg in the first 24 hours (a dose eight times lower than that now recommended and highly unlikely to be effective!).

In 1981 we were joined by Kamolrat Silamut (Oye), and by Dr (now Associate Professor) Pornthep Chanthavanich - (who is now the head of Pediatrics here in the Faculty) in Chantaburi, and in 1982 in Bangkok by Vanaporn Wuthiekanun (Lek) and later Sayan Langla. Work was conducted on cerebral blood flow and metabolism and the blood brain barrier in cerebral malaria, malaria in pregnancy, metabolic dysfunction (particularly hypoglycemia and lactic acidosis) and anemia. We began a series of clinical pharmacology investigations which led to the reappraisal of quinidine as an antimalarial, and the introduction of the quinine loading dose in severe malaria. We were later joined in Chantaburi by Dr (now Professor) Juntra Karbwang, and Dr (now Professor) Rodney Phillips came out in 1983 to join the team from the UK. In Bangkok, in collaboration with the Queen Saovabha Memorial Hospital, and with Associate Professor (now Professor) Pravan Suntharasamai and nurses from the Hospital for Tropical Diseases, studies of new improved regimens for prophylactic and treatment use of the human diploid cell rabies vaccine began. In 1984 studies of snake bite were extended to Trang in the South where bites by the Malayan Pit Viper were a particular problem in rubber plantation workers. Meanwhile in the Hospital for Tropical Diseases, Professor Danai Bunnag kindly allowed us to convert the operating theatre into a specialist intensive care facility for the management of rabies encephalitis. In collaboration with Bamrasnaradura Hospital we began a heroic, but ultimately unsuccessful, attempt to cure rabies encephalitis with massive doses of interferon. I left Thailand in 1984 for two years to work in the UK and USA. During this time the "up-country" malaria study site changed from Chantaburi in the east of Thailand to Paholpolpayuhasena Hospital, Kanchanaburi in the West of Thailand. Studies continued on the pathophysiology and treatment of falciparum malaria and snake bite, and in Bangkok on improved rabies vaccine regimens. The unit was joined in 1984 by Dr May Ho, a clinical immunologist now at the University of Calgary, Dr Wichai Supanaranond (now head of the Department of Tropical Medicine), and in 1985 Dr Yupaporn Wattanagool. David, Mary and Rodney returned to the UK in September 1986 and I took over running the Unit.

We started community based malaria studies in the camps that had been set up for displaced Karen people on the north-western border. These were run (as they are today) by Dr Francois Nosten, formerly of Medécins Sans Frontières, who had helped to set up the program of medical assistance for this rapidly expanding population (then 8,000, now 120,000!). Malaria was the principle cause of morbidity and mortality in this community and multi-drug resistance was a particular problem. The research program started in September 1986 with a placebo-controlled evaluation of mefloquine prophylaxis in pregnancy. The Shoklo Malaria Research Unit was a departure from our previous hospital based studies, as it required the study team to live and work continuously with the population, and the study sites were in difficult and sometimes dangerous locations.

On the other side of Thailand, in August 1986 we began a long-term collaboration with Dr (now Professor) Wipada Chaowagul and her colleagues in the Department of Medicine, Sappasitprasong Hospital, Ubon Ratchathani on melioidosis [infection with *Pseudomonas* (now sadly reclassified as *Burkholderia*) *pseudomallei*]. We were soon joined by Dr David Dance (clinical microbiologist) and Dr (now Professor) Tim Davis (physician), and also Dr (now Professor) Sasithon Pukrittayakamee who had earlier completed her D Phil at Oxford University. In Ubon Ratchathani we began what has been the longest clinical collaboration in our twenty year history with a series of studies on the epidemiology, diagnosis, and management of melioidosis - an infection which comprised then as it does today 20% of community acquired septicemias admitted to this busy 1,100 bed hospital. We were fortunate to have early successes reducing the mortality of severe melioidosis by half, from 80% with the "conventional" four drug regimen, to 40% with single agent ceftazidime. We were also able to develop simple techniques for culture and identification of *B. pseudomallei* which were applicable in a routine laboratory.

In 1988, together with Dr Chaisin Viravan (former Director of the Hospital for Tropical Diseases), we began work on chancroid and lymphogranuloma venereum at the Bangkok Metropolitan STD hospital at Bang Rak. This led to simple methods for differentiating *Lymphogranuloma venereum* and *Haemophilus ducreyii* as the cause of inguinal buboes. However HIV awareness led to a dramatic decline in the number of patients presenting to STD clinics, and this work stopped because of lack of cases in the early 1990s. In 1989 Dr Yupin Suputtamongkol became the first Wellcome-Mahidol Fellow and began five-years of research work on malaria and melioidosis.

In 1988 Feiko ter Kuile joined Francois in Mae Sot, and the local team there began to expand as more Karen staff were recruited to support the expanding studies. Mefloquine resistance was beginning to affect treatment responses in falciparum malaria

and a series of studies were started to optimize treatment. These very large community-based antimalarial drug comparisons synergised well with those conducted in the Hospital for Tropical Diseases. They led first to the replacement of the triple mefloquine-sulphadoxine- pyrimethamine combination by high dose mefloquine alone, and later to the general introduction in the refugee population of the three day artesunate-mefloquine regimen in mid 1994. Before this the Shoklo Unit had been joined in 1990 by Dr christine Luxemburger, and later by Dr Grainne Dolan, and in 1993 by Dr Ric Price, and had begun preparations to test the SPf 66 malaria vaccine. This was a collaboration between the Faculty of Tropical Medicine and US AFRIMS, and this, as with all the studies in the Shoklo Unit, was overseen by the then Dean, Professor Tan Chongsuphajaisiddhi. The Spf66 vaccine program involved safety and immunogenicity testing in the Faculty, and descriptive epidemiology studies in Shoklo before the trial itself. Following vaccine administration 1,349 children were visited every day for 15 months; a huge logistical exercise. Unfortunately the vaccine proved ineffective!

In 1990 David Dance returned to the UK to take up a senior lecturer position at the London School of Hygiene and Tropical Medicine and Tim Davis returned to Australia to take the chair of medicine in Perth. Meanwhile Dr Imelda Bates, a hematologist/malariologist from St Georges Hospital in London came out for a year to help us with our malaria studies. In early 1991 Dr Sanjeev Krishna took over from Imelda and Dr Mike Smith took over as clinical microbiologist, and the technical capability of our microbiology team was soon strengthened further by the arrival of Mandy Walsh. In Ubon Ratchathani clinical trials led to improvements in the maintenance treatment of melioidosis, with longer treatment courses reducing the relapse rate three-fold. The diagnosis of the infection was enhanced by the development of rapid, non-culture techniques. Epidemiological studies conducted by Dr Yupin showed the importance of underlying disease (notably diabetes and renal failure) as predisposing factors for melioidosis and defined the incidence of the infection. Yupin Suputtamongkol also completed a successful MSc in Epidemiology at the London School of Hygiene and Tropical Medicine. The development of techniques for environmental isolation of *B. pseudomallei* provided epidemiological data which explained the geographical distribution of disease, and also led subsequently to the discovery (by Vanaporn Wuthiekanun) of a non-virulent biotype in the environment, which is genetically very close to the virulent organism, and may well be a separate species.

Meanwhile in Kanchanaburi we continued to try and understand how falciparum malaria killed people, and to quantitate the response to drug treatment so that antimalarial drug regimens could be improved. One of the most important developments in this period was the introduction of the artemisinin derivatives for the treatment of malaria. These drugs, which originated in China, were tested extensively by the Department of Clinical Tropical Medicine in the Hospital for Tropical Diseases in Bangkok, by our hospital based team in Kanchanaburi, and in large community based trials by the Shoklo Unit. Cumulatively this has been the largest research experience with these exciting new drugs. The artemisinin derivatives proved the most effective of all antimalarials and they were also remarkably well tolerated. In 1994 rebuilding in Kanchanaburi Hospital led us to move our up-country malaria studies further west to Sangkhla Buri. In that year Dr Brian Angus replaced Sanjeev Krishna, who returned to the UK to take up a consultancy at St George's Hospital.

In the last five years the R Shoklo team has expanded with the arrival of Dr Rose McGready, and Alan Brockman (both from Australia) and Dr Michele van Vugt (from Amsterdam). In early 1996 the security situation deteriorated around Shoklo and we were forced to relocate the unit's center of activities to Mae La camp approximately 50 km north of the town of Mae Sot. A Task-Force was also set up to monitor malaria in all the camps along the border and to provide advice and, if necessary, assistance in malaria control to the refugee population of nearly 120,000 people. Yupin completed her five year fellowship and moved to take a Faculty position at Siriraj Hospital. Meanwhile in Ubon, Mike, Brian and Mandy expanded the microbiological studies to include invasive fungal infections in patients with AIDS (whose numbers were increasing rapidly at this time). Our analytical capability was strongthened considerably by the arrival of Juli Simpson, a statistician and mathematician. In 1996 the hospital based malaria research moved from Sangkhla Buri to Mae Sot Hospital, where we work together with Dr Ronatrai Ruangveerayuth and the department of medicine. In the same year Dr Andy Simpson took over as our clinical microbiologist and Dr Paul Newton replaced Brian Angus as our clinician investigator. Mandy Walsh left to join the Wellcome Unit in Malawi, and was replaced in 1997 by Paul Howe, who in turn was replaced in 1999 by Andy Ramsay.

We have a long standing and fruitful malaria

research collaboration with Professor Rachanee Udomsangpetch at the Faculty Science, Mahidol University. We were fortunate in 1997 to recruit one of her postgraduate students Dr Kesinee Chotivanich (Nok) to run our laboratory malaria research activities. In 1998 Dr Wirongrong Chierakul became the second Wellcome-Mahidol Fellow, and in 1999 Andy Ramsay came from Tanzania via the Royal Free Hospital, to replace Paul Howe.

Today the unit continues to work on the north western border, in Ubon Ratchatani, and in Bangkok. The deployment of combined artesunate-mefloquine as first line treatment for falciparum malaria in the refugee camps has had a dramatic effect on incidence and also resistance. *P. falciparum* transmission has all but been eradicated from the refugee camps, and mefloquine sensitivity has improved. This experience has proved very influential in determining the drug policies for the global Roll Back Malaria initiative. The research unit still sees and treats a considerable amount of malaria on the western border imported from around the camps and amongsts the large migrant laborer population. The impact of both vivax and falciparum malaria on pregnancy and on infant development continue to be studied, and work is also being conducted on thiamine deficiency (previously a major cause of infant death) and tuberculosis (an uncontrolled problem on the border). In Bangkok we collaborate actively with several Departments of the Faculty of Tropical Medicine, notably Professor Sasithon and her group, Assistant Professor Varunee Desakorn in the Department of Clinical Tropical Medicine, and Associate Professor Emsri Pongponratn and colleagues in the Department of Pathology. We conduct laboratory work on *Plasmodium falciparum, Plasmodium vivax, Burkholderia pseudomallei, Crypt ococcus neoformans* and *Penicillium marneffei.* We also provide laboratory support for Associate Professor Punnee Pitisuttithum's work on cryptococcal meningitis which is conducted at Bamrasnaradura Hospital. Hospital based clinical studies continue in Ubon Ratchatani and Mae Sot. This collaborative research program is overseen by a Steering Committee of the Faculty of Tropical Medicine chaired by the Dean, Professor Sornchai Looareesuwan. It has received solid backing at the highest levels from Mahidol and Oxford Universities and unwavering support from the Wellcome Trust. The collaboration has provided research opportunities for many Thai and foreign scientists and physicians and has produced over 450 scientific papers in the past twenty years. The results of this research have been very influential in determining current recommendations for the assessment and treatment of both severe and uncomplicated malaria, and melioidosis. It has been hard work, and like everything, it has had its ups and downs, but I think we all feel it has been worth it!