

SPECIAL REPORT

OVERVIEW OF RESEARCH AT THE INSTITUTE FOR MEDICAL RESEARCH, KUALA LUMPUR, ON ITS NINETIETH ANNIVERSARY

M Jegathesan*

Institute for Medical Research Kuala Lumpur 50588, Malaysia.

HISTORICAL PERSPECTIVE

The Institute for Medical Research began as the Pathological Institute in the town of Kuala Lumpur, the capital of the State of Selangor and of the Federated Malay States. The decision to establish this institute was implemented in 1900 by Sir Frank Swettenham, the Resident-General of British Malaya. The idea was mooted a few years earlier at the Conference of Berlin where the British, Dutch and French thought that it would be timely to establish, simultaneously, medical research institutes in the respective colonies. The *raison d'être* was to improve the living standards of the native populations through improved health status.

In the case of the British, the Liverpool and London Schools of Hygiene and Tropical Medicine had been started by 1899: it was decided that the proposed institute for Malaya would be an offshoot of the London School of Hygiene and a young Canadian staff member, Dr Hamilton Wright was despatched to Kuala Lumpur to start and to run the Institute. He earnestly set about his task and the Institute opened its doors in February 1901. In six months the name of the Institute was changed to that of the Institute for Medical Research, the name that we proudly carry till today.

From its beginning, the role and scope of the Institute's work was wide and varied and composed of an intricate and fluctuant mix of diagnostic, investigative and consultative services, research and training. This was both by design and chance in view of the needs of the Ministry of Health and its

services of which the Institute was an integral part.

Throughout its 90 year existence the Institute has contributed significantly in many areas to the development and progress of the health services in this country - some of them measurable, some intangible. This paper will concentrate essentially on its research activities and achievements although inevitably cross reference will be made to developments and contributions in other areas.

Milestones

The 90 year history is indelibly marked by significant milestones and events which have influenced and contributed towards the evolution of the Institute and shaping it to its present form. Some of these are listed below:

During the first 10 to 15 years of the Institute's history of research into the problems of *beri beri* and malaria, significant achievements were accomplished of which the Institute today is proud. The Institute subsequently expanded its research interests to include a variety of other diseases. Work however, was interrupted by the two world wars.

1914-1918: During the First World War the British officers were despatched to war duty in Europe.

1942-1945: During the Second World War IMR activities were initially evacuated to Singapore. With the fall of Singapore, IMR British officers were interned. Meantime in Kuala Lumpur, the Japanese Occupation Government appointed two Japanese directors to administer the Institute, albeit with reduced scope.

1948: By intergovernmental agreement, the United States Army Research Unit (USAMRU) was established in the IMR. This marked the start

* Dato' Dr M Jegathesan is the Director, Institute for Medical Research, Kuala Lumpur 50588, Malaysia. This Special Report is adapted from his address on the occasion of IMR's ninetieth anniversary celebration, 23-25 June, 1992.

of a 41 year collaborative program that was to prove highly productive, especially in the area of scrub typhus and latterly in malaria.

1957: On August 31st 1957, Malaya became independent and this year signified the start of gradual Malayanization of the Institute.

1960: The University of California International Center for Medical Research (UC ICMR) GW Hooper Foundation research unit was established. This was the start of a 20 year collaborative program that was highly productive in the areas of parasitology, hemoglobinopathies and behavioral science.

1966: The Ungku Omar era marked the consolidation of Malayanization, the initiation of the growth spurt of the Institute and the intensification of the internationalization of the Institute. Among other things, the following can be attributed to the "Prince"- plans for the physical development of the Institute; the establishment of the School of Medical Laboratory Technology and the establishment of the Rural Health Division.

1967: Another important event in this era of IMR's history was the declaration of the Institute as Malaysia's National Center for Tropical Medicine under the Southeast Asian Ministers of Education Organization (SEAMEO) in August, 1967. The SEAMEO-TROPMED program will be celebrating its 25th Anniversary this year.

1970's: During the 1970's, laboratory services were decentralized with the establishment of hospital pathology laboratories and the IMR was to concentrate on specialized diagnostic tests.

1978: On 8th August 1978, an Agreement was signed between the Government of Malaysia and WHO designating the IMR as a WHO regional Centre for Research and Training in Tropical Diseases and Nutrition. This heralded the start of an era of institutional strengthening, and research capability strengthening through improvement of physical facilities, procurement of equipment, consultants, training fellowships, research grants and courses in research methodology. Significant outputs that have resulted from these strengthening activities include research publications, training, consultative services and the setting up of two collaborating centers, viz the WHO Collaborating Centre for Taxonomy and Immunology of Filariasis and Screening and Clinical Trials of

Drugs against Brugian Filariasis (since 1981) and the WHO Collaborating Centre in Medical Entomology for the Ecology and Control of Vectors of Malaria, Filariasis and Dengue (since 1985).

1986: The Ministry of Health formalized its Research Program. The Director of IMR doubled up as the Program Director for Research in the Ministry of Health. This was to enable the strengthening and better co-ordination of all research activities under one program. Funding for the program was obtained from the regular budget of the Ministry of Health. Health research in the country then was coordinated by the National Council for Scientific Research and Development (NCSRD/MPKSN).

1988: The Government initiated a special fund for R and D under a mechanism termed "Intensification of Research in Priority Areas (IRPA)". This changed the face of research in the country and made available approximately an additional 3 million Malaysian ringgit a year for the Institute.

Physical development

Paripassu with the milestones runs the physical development of the Institute as follows:

1928: The Institute expanded to accommodate a South Block for the Administration, the Divisions of Pathology, Bacteriology and a Library. This block is currently the Biomedical Museum.

1953: A Central Block was built which housed the British Colonial Medical Research Team, the United States Army Research Unit, the Divisions of Medical Zoology and Virus Research, the new Library and a Lecture Theatre.

1977: Completion and occupation of the "New Building" costing approximately M\$18.2 million.

1981: The IMR Snake Farm was established at Sungei Batu Pahat, Perlis.

RESEARCH ACHIEVEMENTS

Research, which remains the most important function of the Institute, has over the years resulted in several significant findings and publications. In addition to scientific papers, the IMR has also produced a number of technical reports, scientific publications and technical books.

During the period 1900-1975, IMR's research activities and notable achievements have been thoroughly reviewed in the two anniversary year-

books, "Fifty years of Medical Research in Malaya, 1900-1950" by Dr JW Field and the 75th Anniversary Year Book entitled "Seventy-five years of Medical Research in Malaysia" 1900-1975 by Dr GF de Witt. Of the numerous achievements attained by IMR during this period of time, the three most notable were:

- 1) Research into the cause and treatment of beri beri
- 2) Research into the parasitology, diagnosis, treatment and control of malaria, and
- 3) Research into the vector biology, ecology and treatment of scrub typhus.

To-date the IMR has 16 research programs and highlights of the research activities of the various programs are discussed below under the various sub-headings. However, some of the more significant research achievements are as listed:

1) The research efforts of the IMR in filariasis, over the preceding years, formed the basis of the National Filariasis Control Program that began in 1961.

2) In 1979, work done at the IMR led to the development of the Ministry of Health's Disinfection and Sterilization Policy.

3) In 1981, a team at the IMR succeeded in culturing the human parasite *Brugia malayi* in an *in vitro* system from the infective larval stage (L3) to the fourth (L4) and fifth (L5) stages.

4) Between 1981 and 1983, a hitherto undiscovered species of the schistosome parasite, *Schistosoma malayaniensis*, was described. This schistosome was found in the riverine areas of Kuala Koyan in Pahang.

5) In 1983, it was established that the common local species of leaf monkey *Presbytis melalophos* could serve as an excellent model in drug trials for the treatment of filariasis.

6) In 1989, a local strain of *Bacillus thuringiensis* was discovered, which was more potent than the internationally accepted *B. t. israeliensis* for the biological control of mosquitos.

OTHER HIGHLIGHTS

Malaria

Before the 1980s, the mainstay of research in

malaria was chemotherapy. Various drugs such as maloprim, chloroquine and primaquine were tested for the radical treatment of malaria due to *P. falciparum*, *P. vivax*, *P. malariae* or mixed infections. Also, with the emergence of drug resistant *P. falciparum*, chemotherapeutic studies were carried out in Orang Asli patients at Gombak Hospital to enhance knowledge on the treatment of chloroquine resistant falciparum malaria. Therapeutic studies with Fansidar showed it to be less effective for the treatment of *P. vivax* compared to *P. falciparum*.

In recognizing the problem of drug resistant *P. falciparum*, efforts were made as early as 1979 to culture the parasite *in vitro*. In 1982, the Institute successfully established various local strains of *P. falciparum* using the *in vitro* culture technique introduced by Trager and Jensen in 1975. These cultures have been used extensively for the *in vitro* testing of known antimalarials as well as potential antimalarial compounds. In addition, the Institute has conducted numerous studies using the WHO *in vitro* microtest kit to monitor the extent of drug resistance of *P. falciparum* in various parts of the country. Primate and rodent models of malaria have also been established for the *in vivo* testing and screening of potential antimalarials.

With the development of the *in vitro* culture system for *P. falciparum*, sufficient quantities of antigens were made available for immunological studies. This has led to the establishment of the indirect fluorescent antibody test (IFAT) and the enzyme-linked immunosorbent assay (ELISA) as seroepidemiological tools which are particularly useful in the monitoring of control programs. Epidemiological field studies were carried out among Orang Asli in malaria endemic areas to assess the correlation between immunological experiences of these communities as measured by the IFAT and ELISA with that of parasite rates and densities. Hopefully these studies will also provide important baseline data for future evaluation of a malaria vaccine. Other studies carried out among the Orang Asli were aimed at determining the appropriate methods for control of malaria.

In line with our efforts to produce more sensitive and specific seroepidemiological tools, monoclonal antibodies against *P. falciparum* and *P. cynomolgi* schizont antigens were produced using hybridoma technology. A sandwich ELISA using these mono-

clonal antibodies showed reasonably good sensitivity. With the introduction of biotechnology to the Institute, molecular approaches to the study of parasites included cloning of local isolates and production of DNA probes for various species of malaria parasites.

Filariasis

Earlier research in filariasis was associated with the prevalence, transmission, treatment and control of the disease. However, the drug diethylcarbamazine citrate (DEC), though effective in the treatment of both *Brugia malayi* and *Wuchereria bancrofti* infections is not easily acceptable due to its side effects. Chemotherapeutic trials with other potential drugs *eg* levamisole and mebendazole were conducted together with studies on the epidemiology and transmission of periodic and subperiodic *B. malayi* in order to find a more effective treatment for filariasis and better control or eradication measures against the vectors of this disease. The use of DEC for chemoprophylaxis against *B. malayi* was also investigated.

As a WHO Collaborating Centre for screening and clinical trials since October 1981, the IMR has provided facilities for the tertiary screening of filaricidal drugs in *B. malayi* infection of non-human primates. It has successfully established the *Presbytis* spp. monkey - *B. malayi* model for this purpose and to-date, the Institute has contributed immensely to WHO's efforts in the search for more effective antifilarial compounds. A number of potentially useful compounds have been identified of which Ivermectin is one. The Institute has recently completed a clinical trial for this drug in Malaysian patients infected with *B. malayi* and results show this drug to be effective at a single dose in reducing the microfilarial rate to a significantly low level.

A significant breakthrough in research into the biology of filarial parasites was achieved in the *in vitro* culture of *Brugia* spp. infective larvae using monkey kidney cell line (MK-2) and RPMI 1640 culture medium supplemented with human serum. This system will provide secretory, excretory and somatic antigens necessary for immunodiagnosis and other immunological studies in filariasis. Also, it allows the *in vitro* testing of potential filaricides.

In the search for better immunodiagnostic techniques, a number of monoclonal antibodies

specific to filarial antigens has been developed. These monoclonals are being used in the ELISA for antigen detection in sera of infected humans and animals. DNA probes for *B. malayi* are also being developed as seroepidemiological tools and the evaluation of a DNA probe, pBm15 developed at Harvard University, USA has been carried out in the field to assess its sensitivity and specificity.

Other parasitic diseases

Other than malaria and filariasis, research into several other parasitic diseases has been carried out by the Institute. The major diseases include soil-transmitted helminthiasis, amebiasis, schistosomiasis, toxocarosis and toxoplasmosis.

Studies on soil transmitted helminths were particularly aimed at determining the prevalence rates of different helminthic infections in various communities and carrying out chemotherapeutic trials with anthelmintics to obtain the optimal treatment regimes for individual as well as mass treatment. More specific studies involved the identification of factors responsible for the prevalence rates of these parasites in order to determine priorities needed for a co-ordinated control program.

Interest in schistosomiasis began as early as 1976 when an Orang Asli tested positive using the COPT test. Subsequently, schistosome eggs from various tissues were recovered from a number of Orang Aslis at autopsy. Studies were conducted to identify the snail and vertebrate hosts of the Malaysian schistosome. Morphological studies on the Malaysian schistosome revealed a new species which was named *Schistosoma malaysiensis* and this species appeared to be more similar to *S. mekongi* than *S. japonicum*. Surveys carried out over the years have shown that schistosomiasis is not a public health problem in the country.

The main objective of studies carried out on amebiasis was to determine the prevalence of this disease in the country. Studies on *Giardia* were aimed at understanding the epidemiology and zoonotic transmission of this parasite while research on *Cryptosporidium* was undertaken by the Institute as this parasite recently became attributed as a common cause of diarrhea in man. Two other parasitic diseases that are also being studied are toxoplasmosis and toxocarosis. The Institute hopes to develop rapid diagnostic kits for these two

diseases through the use of purified antigens and monoclonal antibodies.

Human nutrition

Research activities in human nutrition were aimed at providing a constant up-date of food and nutrition issues in the country. Data and information from these studies would serve as inputs to the relevant authorities for the implementation of appropriate intervention programs and activities. Over the past decade, several thrust areas have been identified.

In an effort to identify the nutritional problems of rural communities, a number of nutritional surveys were carried out in several villages in Peninsular Malaysia and Sabah. Such studies helped in understanding the etiology and estimating the magnitude of nutritional problems in these under-served communities. Another study conducted in Kampung Gajah, Perak and several villages in Kota Bahru, Kelantan was aimed at identifying areas with health and socio-economic problems and providing solutions through community participation.

Various studies on food consumption and pattern in communities have revealed a host of factors that could contribute towards the poor nutritional status of children and nutritional well-being of women. Two areas of study were undertaken by the IMR. The first was an infant feeding study to assess the mothers' knowledge and attitudes towards infant feeding practices prior to delivery while the second study involved a survey on the comparative food consumption and pattern in selected Chinese New Villages, Malay kampungs and Indian estates. In addition to these general surveys, other studies have dealt with specific nutrient deficiencies such as anemia in pregnant women and iodine deficiency goiter.

Studies with primary school children were conducted to examine the role of intestinal parasites such as *Ascaris*, *Trichuris* and hookworm in malnutrition and evaluate the nutritional impact of the school supplementary feeding program. Attention was also given to the nutritional excesses among urban communities. The prevalence of coronary heart disease risk factors was investigated amongst a group of urban executives. Nutritional studies into the role of oil were undertaken.

The Institute in collaboration with several other institutions in the country, took on a systematic approach to arrive at a comprehensive food table for use in the country. At the same time, the Institute established linkages with various regional networks, eg ASIAFOODS, ASEAN Foods, Asia-Pacific Food Analysis Network to promote the generation of food composition data. Other studies into the nutritional value of foods included the analysis of cholesterol, dietary fiber, available carbohydrates, carotenoids and vitamin A in locally available foods.

In the last decade, greater emphasis has been given to studies on food safety. As a result, large scale studies into the problems of contamination of foods by lead and boric acid have been carried out while the problem of aflatoxin contamination is still under study.

Environmental impact assessment

Since 1978, the Institute has participated in a number of Environmental Impact Assessment studies on hydro-electric dam projects for example, the Kenyir and Tembilang dams. The medico-ecological studies conducted by the Institute include determining the type of diseases present and their prevalence, assessing the effect on dams on the transmission of these diseases and providing recommendations such as the resettlement of populations at risk in and around the dam area.

Vector control

Research activities on vector control conducted by the Institute were linked to the research priorities of WHO. During the 1970s till the early 80s, research efforts were concentrated on studying the bionomics of known malaria, filariasis and dengue vectors to arrive at better control methods. At the same time, new vectors were incriminated and laboratory confirmation of these suspected vectors was carried out. Important malaria and filariasis vectors were colonized in the laboratory to enable further research to be conducted on them. In response to WHO's recommendation that indigenous strains of *Bacillus thuringiensis* H-14 and *B. sphaericus* were highly desirable as biological control agents for mosquito vectors from the viewpoint of ecological considerations and feasibility of production using local waste, the Institute embarked on studies to isolate these bacteria and characterize

their activity against various mosquito vectors using laboratory bioassays. To-date, a number of local strains of *B. thuringiensis* and *B. sphaericus* have been isolated from various habitats throughout Malaysia. A pilot study to evaluate one isolate, *B. thuringiensis* H-14 (IMR-BT-8) in Selayang, Selangor against *Mansonia* indicated that the larval population appeared to be affected only marginally although laboratory assays showed that this isolate is toxic to *Mansonia*. The mode of delivery of the bacteria to the vector has therefore to be improved. Studies to identify cheap and locally available wastes that could be used to produce indigenous isolates of *B. thuringiensis* through fermentation biotechnology are on-going.

Apart from looking for biological agents for control of vectors, the Institute also performed studies to identify various chemicals that were effective against insect vectors like mosquitos, houseflies and cockroaches. Cytogenetic and isoenzyme studies were undertaken to differentiate vector and non-vector mosquitos belonging to the same complex. This information is relevant for control of the mosquito vectors.

Due to the fact that biological and chemical control of disease vectors was difficult to achieve, research shifted to looking into the use of various methods for personal protection against these vectors. Such measures include the use of permethrin impregnated bednets, repellent soap and DEET impregnated anklets and headbands and wristbands.

Bacterial diseases

A major part of the Institute's research in bacterial diseases has been concentrated on elucidating the medical importance of newer bacteria in our country for example, new strains of *Escherichia coli*, *Legionella* and *Campylobacter* which have been reported to cause diseases in other countries.

A significant achievement in research efforts to develop new diagnostic tests for various pathogens was the development of a modified immunoperoxidase test for the diagnosis of rickettsial diseases. Subsequently, a compact field test kit was produced and this kit is currently being used by 10 laboratories in the country. In addition, comparative studies are being carried out to assess commercially available test kits for the detection of pathogens.

Another important research activity is the surveillance of antibiotic resistance of different phage types of *Salmonella typhi* and serotypes of *Salmonella*. Studies conducted from 1980-1987 showed that only 8 out of 6,451 (0.12%) strains of *S. typhi* were chloramphenicol resistant indicating that chloramphenicol still remains a first-line choice of antibiotic for typhoid fever in Malaysia.

Viral diseases

Studies on dengue continue to be a major research activity of the Institute and the main areas of thrust include efforts to document the epidemiology and risk factors of the disease in the country as well as to evaluate and develop diagnostic tests that are suitable for field application for example, the IgM ELISA and the Dengue dot-blot tests. In addition, biotechnological techniques such as recombinant DNA and PCR are being employed for the development of better diagnostic methods.

The TORCHES program that was initially started to identify important congenital diseases affecting newborns is now in its third phase. Having identified rubella as the most important congenital disease (Phase 1), studies undertaken in Phase 2 looked into the epidemiology and identified risk factors of rubella and other important diseases under this program. In Phase 3, mass immunization of rubella was introduced under the Expanded Immunization Program of the Ministry of Health since 1986 and present research activities include follow-up and monitoring of the congenital abnormality rate to determine the effect of mass immunization.

For AIDS, the Ministry of Health is continuously informed of research results of epidemiological studies conducted by the Institute and evaluation of new test kits to facilitate better management of this disease.

Cancers

The Institute's approach to research in cancer is two-pronged, namely, to study the common cancers in the country at the epidemiologic and molecular biology levels. In the former, a descriptive study of common cancers in East Malaysia has been completed and a hospital-based registry of leukemias and allied blood disorders has been

initiated to obtain a nation-wide database for patient management and public health purposes. The Institute being the only center in the Ministry of Health to perform routine oral histopathological diagnostic services for all hospitals in Malaysia is in the process of setting up a registry for oral cancers in the country to be used in the management, research and prevention of these cancers. At the molecular level, DNA technology has been successfully applied to the study of oncogenes in chronic and acute myeloid leukemias. *In vitro* culture studies of leukemic marrow stem cells performed demonstrated a close relationship between growth pattern and clinical behavior.

Other research activities included a study to evaluate pre- and post-bronchoscopic brushings in the diagnosis of lung cancer and another study to compile national statistics on cervical cancer screening.

A significant research project undertaken by the Institute under the cancer program was a study in an animal model to investigate the protective effect of palm oil and/or beta-carotene on skin carcinogenesis. This study is the first of its kind conducted in the country and may mark a series of further studies involving the country's prime agricultural product and its potential benefit to consumers.

Blood disorders and genetics

Research in this area is centered on studies of thalassemias in local populations. A new dimension to these studies is the use of DNA technology for the identification of exact genetic lesions found locally which are responsible for the varied clinical states. So far, a total of 11 different mutations have been observed and these studies raises the hope that DNA probes may be used to detect the presence of these disorders in clinical samples. It is also hoped that clinical diagnosis at the prenatal level will be made possible with the use of the new polymerase chain reaction (PCR) technology together with *in vitro* globin chain synthesis studies.

Specialized diagnostics

Although research is the main function of the IMR, the Institute contributes significantly to the diagnosis of various diseases in the country through specialized tests. A number of divisions in the

IMR serve as central reference laboratories to the developing peripheral hospital laboratories that were established as a result of the decentralization of laboratory diagnostic services. With this development, it was felt timely that the IMR embarked on studies to look into the selection and evaluation of suitable diagnostic methods and new instrumentation that could be adopted in the local context.

In the field of chemical pathology for example, significant achievements have been made in the development of specialized biochemical assays requiring more sophisticated technical skills and knowledge for the detection of specific proteins for the investigation of myelomas and the detection of drugs of abuse.

Developed tests using radio-isotopic and non-radio-isotopic labels have been employed successfully for the detection of endocrine hormones for fertility studies and presently, studies are being undertaken to develop in-house assays for some of these hormones as well as to establish the use of tumor markers for the prognosis of various cancers.

RESEARCH TRAINING PROGRAM

It is evident that the IMR has made significant contributions in the various fields of research. However, for it to maintain its reputation as a center of excellence in biomedical research, especially research in tropical diseases and nutrition, its research capabilities and infrastructure must be strengthened.

Presently, with the funding through the "Intensification of Research in Priority Areas" (IRPA) mechanism, a significant portion of the IMR's research needs has been fulfilled. The IMR is also proud to note that many of its researchers have been successful in obtaining substantial grants from foreign organizations such as WHO, SEAMEO and JICA for their research work and this in an indication of the recognition given to IMR's research capabilities.

The IMR recognizes that it is crucial for a research institution to have a structured program for human resource development. Towards this end, priority is being given to training of researchers through training courses, seminars and workshops. In this connection, the IMR is proud to say

that numerous medical and scientific officers have been given opportunities to acquire post-graduate qualifications. Of the current 40 research officers in the IMR, 16 possess PhDs, 8 have MSc degrees and many others possess post-graduate professional qualifications in the various disciplines. In addition, fellowships have been offered to train researchers abroad in specialized areas. Nevertheless, these training programs can be further enhanced if IMR researchers are given opportunities for sabbaticals.

In an effort to promote interaction between researchers of the IMR to exchange views and ideas on research findings and to determine future directions in research, journal clubs to keep abreast of the latest knowledge and monthly seminars for researchers to present and discuss their findings are being organized. Researchers are also encouraged to present their research findings at both local and international seminars/conferences as this will not only allow them to share their research findings but also to attract possible collaborative research. Collaborative research is extremely essential to facilitate the exchange of knowledge and expertise and to this end, the IMR has been collaborating with a number of local and foreign

organizations for example, Hooper Foundation, USAMRU, CIDA and more recently JICA, in various fields of research.

CONCLUSION

In conclusion, the IMR can justifiably be proud of its numerous research achievements during the past 90 years.

In view of the fact that new problems will emerge in addition to the prevailing problems we are facing in tropical diseases control and human nutrition, research efforts must be made to obtain solutions to these problems and to devise new strategies for their control and management.

For it to face these new challenges, the IMR must ensure that the existing infrastructure be improved upon and the human resource be continuously developed.

And with confidence and determination the IMR will take on this increasingly challenging role of conducting research to solve health-related problems through the next century in this country.