マレイシア国熱帯病研究プロジェクト事前調査報告書

平成4年3月

国際協力事業団
医療協力部

平成4年3月

国際協力事業団医療協力部

序　文

日本国政府は、平成２年２月及び平成３年４月に実施したマレイシア国に対するコンタクトミッションの調査結果を受け、マレイシア国において熱帯病研究に関する技術協力の可能性を探るべく、事前調査を実施することとした。

国際協力事業団は平成４年２月に調査団を派遣しマレイシア側の技術協力要請の具体的な内容、プロジェクト実施体制、予算措置などの調査を通じ、技術協力の妥当性を検討した。本報告書はその結果を取纏めたものである。

終わりに本調査の任に当たられた団員のご協力に敬意を表するとともに、調査に際し多大のご協力を頂いたマレイシア国政府関係機関、在マレイシア国日本大使館、および外務省初め国内関係機関各位に対し、深甚なる謝意を表する次第である。

平成４年３月

国際協力事業団

理事　西野世界

1. 事前調査団の派遣

1－1 派遣の経緯と目的

平成2年1月、中山外務大臣がマレイシアを訪問した際のマハティール首相との会談時に、日本側より『熱帯病に関連した両国間の医学協力の可能性』について提起した。これを受けて同年2月、ＪＩＣＡはプロジェクト方式技術協力の可能性を調査するためにプロジェクト形成調査団を派遣し、マレイシア側関係者と協議を行った。その後、同年10月要請書が提出されたが、協力要請分野は10項目にもわたるため、再度内容の絞り込みを行うことを目的として、平成3年4月に専門家チームを派遣した。その結果、要請分野の中でＩＭＲ（Institute of Medical Research）を拠点とした熱帯病に係る研究協力がＪＩＣＡのスキームで実現の可能性が高いとの結論に至った。

本調査は上記の経緯を踏まえて、ＩＭＲ側とプロジェクト方式技術協力の詳細を協議するため実施した。

1－2 調査団員の構成

総　　括	小島　荘明	東京大学医科学研究所寄生虫学研究部門教授
ウイルス学	五十嵐　章	長崎大学熱帯病研究所ウイルス学部門教授
協力計画	福原　俊一	東京大学医学部国際交流室講師
医学教育	河野　　浩	文部省学術国際局国際企画課調査係長
技術協力	吉田　　弘	国際協力事業団医療協力部医療協力課職員

1－3　調査日程

日順	月　日	曜日	時　間	ス　ケ　ジ　ュ　ー　ル
1	2月24日	月	09：45 16：00	成田→（ＪＬ７２１便） クアラルンプール着
2	2月25日	火		大使館表敬、ＪＩＣＡ事務所にて打ち合わせ 保健省にて協議
3	2月26日	水		ＩＭＲにて全体会議
4	2月27日	木		ＩＭＲにて個別会議
5	2月28日	金		ＩＭＲにて全体会議 ミニッツ署名
6	2月29日	土	22：45	クアラルンプール→ＪＬ７２２
7	3月1日	日	6：05	成田

1－4　主要面談者

1）保健省

Dr. Jones Varughese	Director, Health Services
En. Mohamed Noor Kasim	International Section

2）ＥＰＵ

Mr. K. Kavanath	Principle Assistant Director, Social Services Section
Mr. Mohamed Shmi Minstam	Assistant Director, External Assistant Section

3）ＩＭＲ（Institute of Medical Research）

Dr. M. Jegathesen	Director
Dr. Mak Joon Wah	Head, Division of Malaria and Filariasis
Dr. K. Inder Singh	Head, Division of Entomology
Dr. Mangalam Sinniah	Head, Division of Virology

4）在マレイシア日本大使館

福田　博	特命全権大使
片上　慶一	一等書記官

5）ＪＩＣＡマレイシア事務所

小泉　純作	所長
小樋山　覚	次長

2. 要　約

1. 保健省との協議

ヘルスサービス部門の局長との協議の中で

・マラリア、デング熱はマ国の保健戦略上で重要な位置を占めていること。

・日本脳炎に関しては未だ十分な疫学的情報が得られていない。

・ＩＭＲで開発された新技術は、コストなどを検討し末端へ普及する。

・今後野外調査を行う際に、マ国の地域医療システムの活用が可能である。

ことを確認した。

2. ＩＭＲとの協議（第１回全体会議）

日本側で用意した質問票により以下について協議及び説明を行った。

①技術協力のスキーム

②プロジェクトの背景

③ＩＭＲの組織について

特に①の中でＩＭＲ側と日本側の間で次の点が問題となった。

・ＩＭＲ側は当プロジェクトを、running cost（消耗品、傭人費など）を含めたパッケージタイプの研究プログラムを日本が援助するものと考えており、ＩＭＲが独自にプロジェクトのためにcounterbudget を組むつもりがないこと。

・ＩＭＲ側は主に専門家の派遣と消耗品の負担を日本側に望んでおり、機材供与はさほど重要視していない。

・ＩＭＲ側はプロジェクト運営に必要な経費のうちadministrative cost については負担することを表明した。

・これに対し日本側は、消耗品の供与は原則として行わないが、現地業務費を含めた全体の予算の範囲内で検討すること、technicianを継続的に雇用はできないが野外調査等で一時的に現地業務費にて対応できること、を説明し了解を得た。

3. ＩＭＲとの協議（個別会議）

１）ENTOMOLOGY部門

２）VIROLOGY部門

３）MALARIA/FILARIA 部門

上記の部門の研究者と意見を交換し技術協力の方向性を検討した。

4. ＩＭＲとの協議（第２回全体会議）

・日本側の原案に基づき、詳細計画の作成をマレイシア側と双方で行い確認を行った。

・各研究内容ごとに双方のカウンターパートについて暫定的な取り決めを行った。

・協議内容をミニッツに取り纏め署名交換を行った。

・また協力内容をロジカルフレームワークにまとめた。

3. カウンターパート機関としてのＩＭＲの分析

1）マレイシアにおける医学研究予算決定のシステム

ＪＩＣＡプロジェクトのカウンターパートであるマレイシア医学研究所Institute for Medical Research（ＩＭＲ）はマレイシア国保健省直轄の医学領域における唯一の中央研究所である。マレイシア（以下マ国）保健省の下、年間 140万マレイシアドルの予算がＩＭＲに計上されている。この予算は、研究以外の研究員給与、交通、通信、試薬などの消耗品、小型の備品などに使われ、その使用は、すべて保健省の管理下に行なわれ、ＩＭＲは保健省に毎月報告しなければならない。またWHO、ＰＯＲＩＭ、ＳＥＡＭＥＯ－ＴＲＯＰＭＥＤ等よりの、研究費としてのファンドについてもすべて保健省の管理下におかれている。

その他に、ＩＭＲを始めとするマ国における医学研究予算として、科学省よりの年間約300万マレイシアドルの予算は、一度保健省を介した後、ＩＭＲがその保健省の代表として、他機関も含めた研究予算の配分を決定し、それを再度提案するという形で科学省に報告するという形式を取っている。

さらにマ国においては、これらの上部機関として、ＥＣＯＮＯＭＩＣ　ＰＬＡＮＮＩＧ ＵＮＩＴ（ＥＰＵ）という組織が存在し、全体的な総括を行っている。

2）ＩＭＲの組織

ＩＭＲの各Divisionのうち、今回のＪＩＣＡプロジェクトに於て、主なカウンターパートとなるのは以下の３Divisionである。

1 : Division of Malaria and Filariasis

2 : Division of Medical Entomology

3 : Division of Virology

今回の事前調査団では、それぞれのDivisionについて、研究実施体制が調査検討された。

1 : Division of Malaria and Filariasis

このDivisionは、Head of DivisionであるMak Joon Wah, M.D. を中心にStephen Ambu, Ph. D., Patricia Lim Kim Chooi, Ph.D., Noor Rain bt. Abdullah, Ph.D., Chong Hen Kee, B.Sc. Normaznahbt, Yahama, M.D. 等の常勤研究員、非常勤研究員、およびテクニシャンにて構成されている。またＩＭＲでのBiotechnology Divisionは、このDivisionに属し他Divisionと共同使用されている。

このDivisionは現在スタッフ人員が少ないために、おもに応用研究を中心として行われており、基礎研究に関して特に技術協力が望まれている。

主な研究プログラムとしては、

1．マラリアの血清疫学

国内での様々な地域において、抗寄生虫抗体、脾臓、鎌状胞子率に対する種々の血清学的分析結果の関連について調べ、それらの分析が果たして血清疫学の目的で使いうるのかを調べる。

2．in vitroで*のPlasmodium falciparum*の薬剤感受性のモニターリング

3．*Plasmodium falciparum*の分離培養

一つの分離株（GombakA）は、in vitroで育てられ間接蛍光抗体法やＥＬＩＳＡ法の抗原株として使用されている。

4．様々なインターベンションプログラムによるマラリアの伝染経路の変化について、また何が最善の伝染経路の変化の指標となるのかを調査、研究する。

5．鎌状胞子、蛇毒に対するモノクローナル抗原の作製。（Noor Rain bt. Abdullah, Ph. D.）

6．1991年より新しいプロジェクトとしてＤＮＡ診断法の確立が始まっている。（Patricia Lim Kim Chooi, Ph. D.）

今回のプロジェクトではマ国側より強い要望が出されている基礎研究の分野の中で、何を研究テーマにするか、両国研究者の協議が行われた結果、以下の２点で協力をすすめていくことで合意に達した。

1．マラリアのＤＮＡ診断法の開発

2．マラリア原虫の防御抗原エピトープ及び、ミトコンドリア遺伝子の解析。

これらの研究に対するマ国側の研究者カウンターパートとしては、ＤＮＡ診断法については、昨年より研究を始めているPatricia Lim Kim Chooi, Ph. D. とStephen Ambu, Ph. D. が、また防御抗原エピトープに関しては、Patricia Lim Kim Chooi, Ph. D. とNoor Rain bt. Abdullah, Ph. D. が予定されている。現在ミトコンドリアの研究についてはマ国側研究者は未定である。

2 : Division of Medical Entomology

医昆虫部門は、K. Inder Singh, Ph. D. をHead of Divisionに、Lee Han Lim, Ph. D., Loong Kok Poay, M. Sc., G. L. Chiang, Ph. D., V. Indra, Ph. D. 等の研究スタッフによって構成されている。

この部門で現在行われている主な研究は、

1．殺虫剤（permethrin）を注入したネットの使用によるマラリア媒介蚊群、住民のマラリア寄生率に対する影響。

2．マ国における日本脳炎（JE）の疫学的調査

3．土着の生物学的コントロールエイジェント（特に原生生物）の分離、スクリーニング、同定と、その公衆衛生学的見地からの蚊のコントロールへの有用性

4．媒介蚊における殺虫剤への抵抗性探知のための高速生化学的テストの開発

5．腐肉中の節足動物の発生の分析とその法昆虫医学への応用

6．ゴミの地域利用による土着の殺蚊性*Bacillus thuringiensis*の生産

7．昆虫学的／寄生虫学的な*Bacillus thuringiensis*のマラリアに対する影響の評価

8．ヤブ蚊中のデングウイルス抗原の検索のためのＥＬＩＳＡ法の開発

これらの研究のうちLee Han Lim, Ph.D. が中心となり*Bacillus thuringiensis*の研究を行っている。

今回のＪＩＣＡプロジェクトでは、医昆虫部門にて、分子生物学的レベルにおけるマラリア媒介蚊の易感受性、抵抗性遺伝子の同定、媒介蚊からのデング／ＪＥウイルスの分離といった研究分野において日本からの研究協力要請がマ国側よりだされている。マ国側研究者の中のG. L. Chiang, Ph. D., V. Indra, Ph. D. は、分子生物学の知識があるため遺伝子の同定の研究にあたり、またK. Inder Singh, Ph. D., Lee Han Lim, Ph. D., G. L. Chiang, Ph. D. 等が、デング／ＪＥウイルスの分離に当たる予定になっている。

3 : Division of Virology

ウイルス部門は、Mangalam Sinnah, M. D. をHead of Divisionに５人の常勤研究者を中心に３名の非常勤研究者、18名のテクニシャンにて研究が行われている。この部門では、今回のＪＩＣＡプロジェクトに対しVijayamalar Balasubramaniam, M. D. と二人のテクニシャンを配置する予定であると表明している。

現在ウイルス部門で行われている研究としては

1．マレイシアにおけるDelta Hepatitisの調査、陰部潰瘍微生物学的検索、HIV antibody testing等を行っている。

2．Tissue Cultureも行われているが、実際には抗体を測る程度であまり行われていない。

3．デング出血熱、デング熱ショック症候群とTumor Necrosis Factor の関係についての研究（M. Sinnah, Ph. D.）

4．デング熱については、その陽性の血清を20年以上保存するといったことを行っている。

日本脳炎に関しては、公衆衛生的な見地からも過小評価されているというのが現状であり、このウイルス部門においてもあまり研究はなされていない。また研究以外でも、その診断技術の一般普及もあまり確立されていない。そのため、マ国における日本脳炎の罹患率さえ的確に把握されていないというのが現状である。今回のプロジェクトでは、デング熱、日本脳

炎の分子生物学、バイオテクノロジーの応用による診断能力の向上、その技術を利用しての疫学調査、デング出血熱の分子生物学的レベルでも病因論の理解といった研究テーマが予定されている。診断法については、Vijayamalar OBalasubramaniam, M. D., 疫学調査については、Mangalam Sinnah, M. D. がマ国側の研究者として予定されている。病因論に関しては、現在未定である。

4. プロジェクト方式技術協力のための計画

4－1　マラリア

前回の調査団の報告に記されているように、熱帯病の診断や防圧あるいは研究に分子生物学的手法を強力に導入したいとのマレイシア側の希望に沿って、あらかじめ作成された計画原案について、マレイシア側研究者と討議した。その結果、マラリアについては、次のような研究計画とすることで合意が得られた。

1）マラリアのＤＮＡ診断法の開発

現在、マラリアの確定診断は、ギムザ染色を施した血液塗抹標本の鏡検によって行われているが、これには熟練が必要である。一方、間接蛍光抗体法や酵素抗体法（ＥＬＩＳＡ）などの免疫診断法も開発されているが、基本的に抗体の検出に頼る診断法は、現在の感染のみならず過去の感染をも反映するものであり、診断的価値よりも、血清疫学的な意味で利用価値が高いと考えられる。そこで、より簡単で迅速に現在の感染を正確に検出することのできる検査法、言い換えれば虫体そのものないしは虫体の構成成分を、直接的にかつ特別の熟練を要することなく検出できる検査法の開発が望まれる。このような感受性と特異性にすぐれた検査法として、本研究計画ではＤＮＡ診断法の開発を試みる。すでに、熱帯熱マラリア原虫については、さまざまなＤＮＡプローブが開発されており、どのようなプローブが診断の目的に合ったものであるか、ＰＣＲ法をもちいて検討するとともに、患者血液よりの原虫ＤＮＡ調整法について検討することとした。特に、マレイシアでは、種々のサルマラリア原虫の存在が知られており、種特異的なプローブの開発は、これらのサルマラリアの診断や疫学的研究にも有用な手段となることが期待される。

2）マラリア原虫の防御抗原エピトープの同定とその性状の解析

最近、アフリカにおいて、熱帯熱マラリアに対する抵抗性と主要組織適合遺伝子複合体（ＭＨＣ）のあるハプロタイプとの間に関連性のあることが見出されているが、マレイシアにおいても、抵抗性患者群の存在の有無とＨＬＡハプロタイプとの関連性について検討し、さらにＭＨＣ関連防御遺伝子の検索を行うこととした。その上で、このような抵抗性患者群のＴまたはＢ細胞の認識する防御抗原エピトープの検索を行い、さらに最終的には防御抗原遺伝子のクローニングを目指す予定である。

3）マラリア原虫ミトコンドリア遺伝子の解析

各発育段階のマラリア原虫について、それらの表面抗原に関しては遺伝子レベルで盛んに

研究がなされてきている。しかし、マラリア原虫にミトコンドリアが存在することは電顕的に確認されているものの、その生理的機能については未だ十分な研究はなされておらず、マラリア原虫のミトコンドリアＤＮＡについては不明の点が多い。マラリア原虫は、蚊の体内では好気的エネルギー代謝を行い、ヒト体内の発育段階においては主に解糖系によりＡＴＰを産生しているものとみられているが、ミトコンドリアに存在することが予想されるこれらに関与する酵素群についても興味深い問題が多い。通常、ミトコンドリアは、独自の環状ＤＮＡを持っている。それは、哺乳類では、13種のミトコンドリア蛋白質と22種のtRNA及び２種のリボソームＲＮＡをコードしており、ヒトでは約16kbのサイズである。これに対し、マラリア原虫においてミトコンドリアＤＮＡと考えられているものは、rRNA、COXI、cytbの３種の遺伝子を含む６kbの環状ＤＮＡである。このサイズは、報告されているミトコンドリアＤＮＡ中で最も小さく、このことは他の遺伝子が核へ移っているのか、または他のオルガネラに存在している可能性を示唆する。これに関連して、最近、spherical body（ＳＢ）に局在する35kbの環状ＤＮＡが注目されているが、その実体は明らかでない。このように、マラリア原虫のミトコンドリアの基礎的研究は、細胞生物学的にも極めて重要である。さらに、ミトコンドリアＤＮＡは、進化速度が核のそれに対して約 100倍速いことから、制限酵素による切断パターンや塩基配列の相違から、原虫の異なる分離株間のタイピングを行うことも可能と考えられる。また、発育段階毎の変化を追求すること、あるいは、コードしている蛋白の種類などヒトと大きく異なる領域について、化学療法の作用点としての可能性を検討することなども、ミトコンドリアＤＮＡの解析によって可能になると考えられる。そこで、本研究計画では、まず、原虫ミトコンドリア画分の調整法を確立した後、ミトコンドリアＤＮＡの分離と全塩基配列の決定を行うこととした。さらに、他の動物のミトコンドリアＤＮＡにコードされ、マラリア原虫６kbＤＮＡにはコードされていない遺伝子の局在性の解析、および各発育段階におけるミトコンドリアＤＮＡ上の遺伝子の発現の解析を行うとともに、病原性、薬剤耐性、地理的分布などに着目した原虫分離株のミトコンドリアＤＮＡによるタイピングを行う予定である。

４）媒介蚊種内変異株の分子生物学的解析

マラリア対策には、これを媒介する蚊の防除も重要な因子となることは言うまでもない。マレイシアにおいては、マラリアの主要媒介蚊である*Anopheles maculatus* には、形態学的には識別困難な種内変異が存在し、マレー半島ではこれがマラリアの主要な媒介者であるのに対し、サバでは*A.maculatus* は主たる媒介者ではなく、他の種類（*A.barabaciensis*）が主にマラリアを媒介する。そこで、本計画では、両地域の*A.maculatus* における差異が、どのような遺伝子によって規定されているかについて検討する。このため変異株のＤＮＡ分離と

全塩基配列の決定、マラリア感受性遺伝子の局在とその発現の解析、遺伝子操作による非感受性株の作製とそれによる感受性株の生物学的コントロールの可能性などについて検討することとした。

4－2　デング・日本脳炎

マレイシア国においてはデングウイルス感染症は重要課題であり、日本脳炎ウイルスの伝播状況も十分には解明されていない。本計画の一環として、マレイシア国におけるデングウイルス感染症並に日本脳炎の防除という目的を達成するために分子生物学的・バイオテクノロジーの技術の応用を計画し、下記の課題について研究を実施する。

1）分子生物学およびバイオテクノロジーを用いた診断技術の強化

a）ＩｇＭ－ＥＬＩＳＡ法の改良

現在ＩＭＲウイルス部では、1991年以来、ＩｇＭ捕捉ＥＬＩＳＡ法を用いて、デング熱（ＤＦ）／デング出血熱（ＤＨＦ）および日本脳炎（ＪＥ）患者の血清診断を行っている。この方法は、1987年にマラヤ大学のS.K.Lam 教授らが発表したもので、その概略は

①抗ヒトＩｇＭ抗体をマイクロプレートに固相化する

②被検血清１μℓを100μℓの稀釈液にマイクロプレート上で添加する。

③デング２型抗原100μℓを加える。

④抗デング２型マウス単クローン抗体100μℓを加える。

⑤ペルオキシダーゼ（ＨＲＰＯ）標識抗マウスＩｇＧ抗体100μℓを加える。

⑥基質を加えＨＲＰＯ反応により発色させる。

の６段階より成っている。反応①、⑤、⑥の試薬は市販されているが、反応③の抗原はウイルス感染マウス脳から庶糖アセトン法で抽出しなければならず反応④に用いる単クローン抗体はLam教授を通じて米国から分与されている。従ってこれらの試薬量の制限によって、本法を用いた血清診断はマレイシア国では専らＩＭＲでのみ実施されており同国の末端の検査室には普及していない。更に、本法の感度と特異性に関しても問題が多く、臨床的に明らかにデングと診断されていてもＩｇＭ－ＥＬＩＳＡ陰性の患者や、臨床的に明らかに他の疾患と診断されていてもデングＩｇＭ－ＥＬＩＳＡが陽性結果を示す例が相当数存在する。

本計画ではこれらのＩｇＭ－ＥＬＩＳＡ法の問題点を解決するために、まず、デングウイルス感染C6／36細胞培養液を反応③の抗原として使用し、さらに高力価のＤＨＦ患者血清からＩｇＧを調製し、ＨＲＰＯで標識後、反応④⑤を一つの段階として行う反応の検出用抗体として使用する。これらの改良によって、抗原調製の簡易化と、反応時間の短縮、操作の簡略化を図る。

C6／36細胞は現在ＩＭＲで継代培養されていないが長崎大学熱帯医学研究所ウイルス学部門から分与できる。

ＩＭＲウイルス部の細胞培養設備を強化するためにバイオハザード安全キャビネット CO_2 インキュベーター胎児牛血清、粉末培地等の供与が必要である。同部には、現在、までマレイシア国各地から検査依頼のため送付された患者血清約５万検体が凍結保存されており、それらを用いれば、本研究は本プロジェクト第１年度に実施可能である。

b）ポリメラーゼ連鎖反応（ＰＣＲ）を用いたウイルス遺伝子の検出と同定

試験管内でＤＮＡ分子の特定部分を短時間で増幅できるＰＣＲ法はウイルスを含む多くの感染症病原体の検出方法として急速にとり入れられている。デングウイルスおよび日本脳炎ウイルスの遺伝子は一本鎖のＲＮＡなので、ＰＣＲ法でこれらのウイルス遺伝子を検出するには、まず逆転写酵素反応によりＲＮＡをＤＮＡに逆転写したのち、通常のＰＣＲ増幅を行わなければならない。長崎大学熱帯医学研究所ウイルス学部門では、１本の試験管ですべての反応操作を行い、かつ、ウイルス特異的プライマーペアを用いるとデングウイルスの検出と型同定が同時に可能な方法を開発し報告した。さらに最近、ＲＮＡ抽出操作を行わなくても患者血清５μℓから直接ＰＣＲの結果が得られる迅速逆転写ＰＣＲ法を開発した。（Rapid RT-PCR）

この研究では、すでにＩＭＲに保存されているデング患者血清中、抗体陰性の検体についてRapid RT-PCRを行い、ウイルス遺伝子の検出と型同定を行うと共に、次に述べるウイルス分離を実施することにより、Rapid RT-PCR法がデングウイルス感染症の迅速診断法として使用できる可能性を検討する。

c）C6／36細胞を用いたデングウイルスの分離

ＩＭＲではマラヤ大学S.K.Lam 教授らの考案した、検体をToxorhynchitinae蚊幼虫に接種する方法でデングウイルスおよび日本脳炎ウイルスの分離を行っている。この方法に用いる蚊幼虫はＩＭＲ衛生昆虫部で飼育されているが、蚊幼虫が入手できない場所ではこの方法は実施できないし、一匹の蚊幼虫に接種できる検体の量が限られており、接種も熟練技術を要する。一方、長崎大学熱帯医学研究所で開発されたC6／36細胞を用いる方法は、細胞培養と無菌操作の技術は必要であるが、熱帯地の多くの場所で応用できる利点がある。

この研究ではデング患者から得られた血清検体を飼育蚊幼虫と、C6／36細胞に接種し、両方法でのウイルス分離成績を比較することによりＩＭＲにおけるデングウイルス分離の標準法を確立する。同時に前述のRapid RT-PCR法を行うことにより、ウイルス分離成績と遺伝子検出成績を比較し、患者の臨床像との比較検討も行う。

2）デングウイルス感染症と日本脳炎の疫学調査

a）デング

デングウイルス感染症はマレイシアを含む東南アジア諸国では深刻な問題となっているが、予防ワクチンは未だ開発途上である。従って、デング感染症の防除対策としては、その流行をできるだけ早期に察知して、媒介蚊の対策を実施することが現在可能な方法である。この業務に関してはＩＭＲの衛生昆虫部が、デングの主要媒介蚊である*Aedes-aegypti* の密度調査を実施している。この研究計画では、現行の監視体制を更に強化するために、適当な観測地点で定期的に*A.aegypti* の密度調査を行うと共に、採集された蚊検体からのウイルス分離とRT-PCR法によるウイルス遺伝子の検出を行う。

b）日本脳炎

日本脳炎は致命率が高く、回復者の約半数も重篤な後遺症を残すことから重視されてきた疾患であるが、マレイシア国において日本脳炎ウイルスの感染がどの程度浸透しているか十分に解明されていない。マレイシア国において将来、予防ワクチン接種などの日本脳炎防除対策が必要であるか否かを判断するための知見を得るために、下記の調査を実施する。

(1) 日本脳炎媒介蚊である*Culey tritaeniorhynchus, Cx.gelidus* の密度を適当な観測地点において定期的に測定し、採集された蚊検体からのウイルス分離と、RT-PCR法によるウイルス遺伝子の検出を行う。

(2) 日本脳炎ウイルスと感受性の動的血清について、日本脳炎ウイルスに対する抗体調査を行う。

(3) 健康住民の年令別抗体調査を行う。

(4) 急性脳炎患者の血清と髄液についてＩｇＭ－ＥＬＩＳＡによる血清診断を行うと共に、髄液についてはウイルス分離と、RT-PCRによるウイルス遺伝子の検出を行う。

3）分子レベルにおけるデング出血熱（ＤＨＦ）の発病機構の解明

デングウイルスに感染した場合、どのようにして重症型のＤＨＦを呈するようになるかという発病機構としては、二次感染説、とりわけ免疫増殖促進説が提唱されてきたが、この説では二次感染患者の中でＤＨＦを示すのは約６％にすぎない事実を説明することは困難である。

この研究では、ＤＨＦの発病機構とウイルス側の要因が関与している可能性を検討するために、同一の流行期と同一地域で重症のＤＨＦ患者、軽症のＤＦ患者、および媒介蚊から分離されたデングウイルス遺伝子の塩基配列を解析する。ウイルスをC6／36細胞で培養後、感染培養液から適当なプライマー付を用いたRT-PCR法で遺伝子を増幅し、大腸菌プラ

スミドにクローニングの後、dideoxy chain-termination 法により塩基配列を解析する。

コンピューター解析により株間の塩基配列を比較すると共に、それから推測されるアミノ酸配列についての比較も行う。ついで異なる年代、異なる地域で分離されたデングウイルスの遺伝子解析からウイルスの変異と地域差を解析する。

この研究は研究計画1）、2）で分離されたウイルス株を用いるのはもちろんの事、すでにマラヤ大学S.K.Lam教授等の研究グループが分離したウイルス株を用いる事も必要なので同教授との共同研究として実施する事が望ましい。

4）マレイシア国におけるデングと日本脳炎に関する診断技術と疫学調査法の普及

ＩＭＲで確立された技術と方法をマレイシア国における標準法として普及させる事により、当該国におけるより正確な患者数、並に疫学情報が得られる事を目的として、必要な検査技術等に対する教育訓練を計画し、実施する。

5. 相手側との協議内容

5－1　IMR

ＩＭＲにおける最初の全体協議においては、日本側調査団長より訪問の目的について説明があった後、協議に入り、本研究協力に必要な備品等は、保守管理の面からもＪＩＣＡマレイシア事務所を通して現地業者から購入することが望ましいことが強調された。しかし、本プロジェクトに要する消耗品等の購入に必要な研究費については、マレイシア側で極力負担する必要のあることが日本側から強く述べられたが、マレイシア側はこの点については難色を示し、結局ＪＩＣＡとしてはこの目的のために総額の約15%程度の支出を示唆することで、この場の討議を先に進めることとなった。そして、マレイシアにおけるマラリア、デング熱、及び日本脳炎の流行状況について説明があった後、具体的な研究計画については個々の研究部門毎に協議することとした。さらに、本研究プロジェクトの結果得られた成果の特許に関しては、その研究に携わった当事者とＥＰＵ及びマレイシアＭＯＨの関係者によりその都度協議することとなった。また、論文等の発表に関しては、ＩＭＲにすでに存在する規定に沿うことで合意した。

このような全体会議を経て、翌日、個々の研究部門を訪問し、上記のような研究計画について、それぞれカウンターパートとなる部門毎に協議した。そして、カウンターパート分析の項にも述べたごとく、日本側の派遣が予想される専門家の領域と、それぞれに対応するマレイシア側の研究担当者の組分けについても相談した。

これらの具体的な研究計画と個別的な協議の後、ＩＭＲにおける最終日に再び所長の出席のもとに全体協議を行った。日本側の作成したlogical frame work原案について検討した結果、かなりの字句訂正はあったものの大筋において双方の合意が得られた。但し、研究遂行のために必要な消耗品、とくに分子生物学的研究を推進する際に必要となる試薬類については、日本側において購入してほしい旨マレイシア側から強い要望が出された。これは、ＩＭＲにはすでに分子生物学的研究を推進するためのハードウエアはかなりのものが用意されているのに対し、上記の試薬類は本研究計画の性格上その根幹をなすことが予想されるとともに、マレイシアにおける購入は科学研究費の裏付けがない限りほとんど不可能であること、一方、本プロジェクトをマレイシア側の国家科学研究費による研究プロジェクトとして同時併願することはできないことなどから出された強い要望であった。logical frame workについては、一応、マレイシア側が、"contribute to the local cost of consumables" ということで了解したが、最後の覚書きの署名の際に再び問題となり、Attached Document には "To make necessary arrangements for the provision of local infrastructure and administration of the project" という表現で記されることになった。

5－2　保健省

Ministry of Health（MOH）

ＩＭＲはＭＯＨに属するマレイシア国唯一の研究機関である。本計画の実施に当り、ＭＯＨの機構と活動を理解するため、本調査団は1992年２月25日ＭＯＨのDivision of Health Servicesを訪れ Dr. Jones Varughese 部長の説明を受け、質疑応答を行った。その結果の概略を下記に記す。

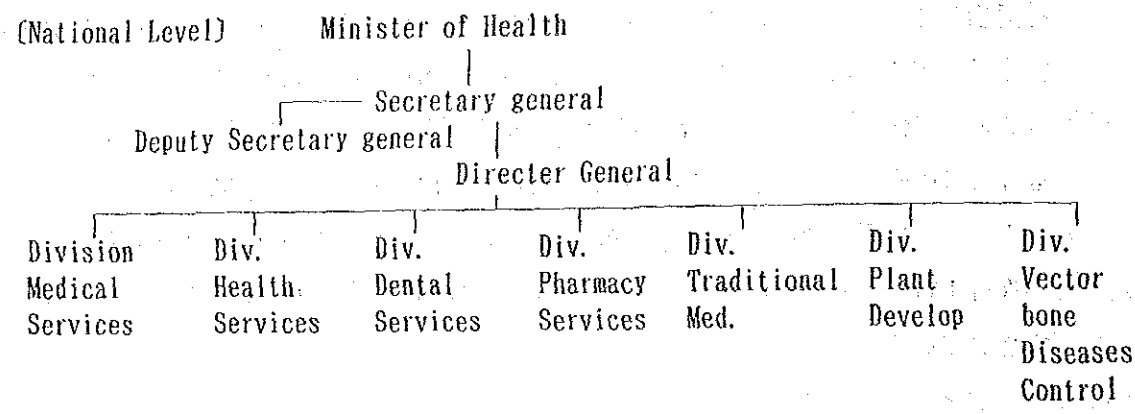
- oマラリアとデングはマレイシア国における保健衛生上の重要課題である。
- o日本脳炎の確認患者数は年間数十名にすぎないが、さらに詳細は疫学的情報を得る必要がある。
- oマラリア患者の大多数はSabah 州で発生しており、近隣諸国からの不法入国者の移住との関連もあり、今後もマラリアの重要性は変らないであろう。
- oマレイシア国ではマラリアとデングは従来ＭＯＨのVecter-bone disease divisionの業務であったが、現在ではgeneral health services systemに総括されて行われている。
- oマレイシア国におけるマラリア対策は大部分の地域ではすでにMaintenance Plase に入っているが、一部の地域では未だattack phaseであり、治療法も問題がある。
- oデングは流行しはじめた頃は大都市の問題であったが、その後、流行地域が拡大して現在では都市部のみならず農村部でも問題となっている。
- oデングの流行は患者発生の記録から約５年毎の周期を示すようにみえる。
- oＩＭＲで開発された技術を末端へ普及することはＭＯＨとしても推奨している。
- oＭＯＨの基本方針は、Primary Health Cure によるHealth to all (by the year2000) である。
- oたとえば Family Healthは現在も重要課題であり、現在の乳児死亡率13／1000は発展途上国では低い部類に入るが、先進国のそれに近づくには更に改善の余地がある。
- o現在、分娩の30%は家庭で行われており、そのうち総分娩の７%が近代医学の訓練を受けていない伝統的な分娩法で行われている事を改善する必要がある。
- o出産後の対策としては助産婦、保健婦による家庭訪問を強化する必要がある。
- o出産前の妊婦の95%に対しては母子対策が行われている。
- o新生児に対する（ＥＰＩ）ワクチン接種率は90%に達しており、Ｂ型肝炎ワクチン接種（３回）も含まれている。
- o全国の医師の50%は民間の医療機関に所属している。
- o農村地域での予防対策はすべて政府機関により実施されている。
- o1960年以降実施されてきたThree-tier Rural Health systemは、1969～71年に実施されたＷＨＯとの共同調査の結果、現行のTwo-tier Rural Health systemに置き換えられた。

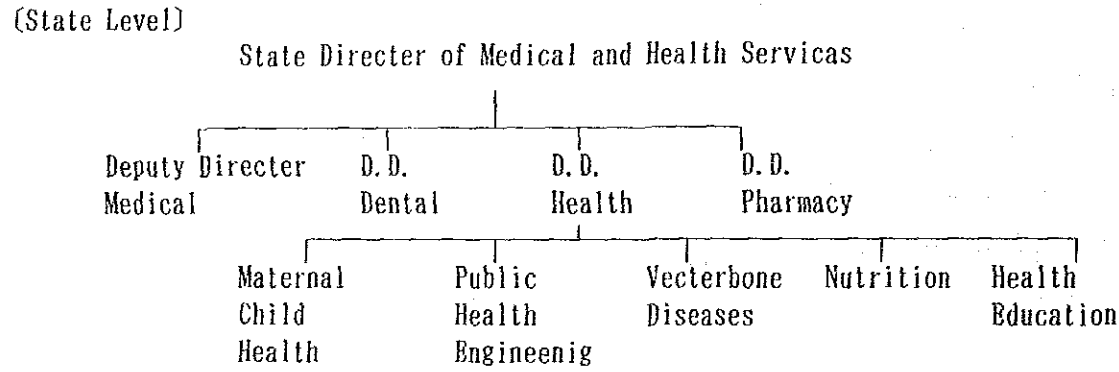
このsystemでは人口15,000～20,000人当り１つの Health Center、人口3,000～4,000人当り１つのKlinik Desa が設置されており、１つの Health Centerは４つのKlinik Desaを担当している。 Health Centerには政府が任命した医師が配属されており、医学部卒業生は一定期間Rural Health Center での勤務が義務づけられている。

このHealth Service System が完備された事により1977～78年現在、マレイシア国半島部では医療サービスを受けていない人口は全人口の7.3％にすぎなくなった。

oＡＩＤＳが最近マレイシア国でも緊急課題となっており、その防除対策が問題である。現在ＡＩＤＳ患者数は約40名であるがＨＩＶ抗体陽性のキャリアは2000名以上いると推定されている。

〔付表〕ＭＯＨの機構図





〔District level〕 Fully integrated
No more division

6. ミニッツ及びログフレーム

MINUTES OF DISCUSSIONS
BETWEEN THE JAPANESE PRELIMINARY SURVEY TEAM AND
THE AUTHORITIES CONCERNED OF THE GOVERNMENT OF MALAYSIA
ON THE JAPANESE TECHNICAL COOPERATION PROJECT
FOR
THE RESEARCH OF TROPICAL DISEASES

The Japanese Preliminary Survey Team (hereinafter referred to as "the Team") organised by the Japan International Cooperation Agency (hereinafter referred to as "JICA") and headed by Dr. Somei Kojima visited Malaysia from February 24th to 29th, 1992 for the purpose of making a study of the request for the Japanese Technical Cooperation Project for the Research of Tropical Diseases (hereinafter referred to as "the Project").

During its stay in Malaysia, the Team exchanged views and had a series of discussions with the Malaysian authorities concerned.

As a result of the study and the discussion, the Team and the Malaysian counterparts concerned came to a tentative understanding on the matters referred to in the document attached hereto for referral for information and approval by their respective higher authorities.

Kuala Lumpur, February 29th, 1992

S. Kojima
.....
Dr. Somei Kojima
Leader
Japanese Preliminary
Survey Team
Japan International
Cooperation Agency

.....
Dr. M. Jegathesan
Director
Institute for Medical
Research, Ministry of Health
Malaysia

THE ATTACHED DOCUMENT

1. PURPOSE AND OBJECTIVES OF THE PROJECT

1) The purpose of the Project is mainly aimed at strengthening research, diagnosis and management of selected tropical diseases in Malaysia.

2) The objectives of the Project are as follows:

(1) to strengthen the use of biotechnology in the diagnosis and management of Malaria

(2) to strengthen the use of biotechnology in the diagnosis and management of dengue fever and Japanese encephalitis.

2. NAME OF THE PROJECT

The Project of Research and Development for Diagnosis of Selected Tropical Diseases.

3. RESPONSIBLE ORGANIZATION

1) The Ministry of Health will bear the overall responsibility for the successful implementation of the Project.

2) The Director of the Institute for Medical Research will be responsible for the administrative and managerial matters of the Project.

3) A Coordinating Committee for the smooth implementation of the Project is expected to be established at the start of the Project according to the following compositions:

(1) Chairman: Director, Institute for Medical Research
Ministry of Health Malaysia

(2) Member: Malaysian side:

- Head, Division of Malaria and Filariasis
- Head, Division of Entomology
- Head, Division of Virology

Japanese side:

- Team Leader of the Japanese experts
- Coordinator
- Japanese experts
- Other personnel to be dispatched by JICA
- Resident Representative of JICA Malaysian Office

(3) Observers:

- Representative(s) of the Embassy of Japan
- Representative(s) of the Ministry of Health
- Representative(s) of the Economic Planning Unit

4. MEASURES TO BE TAKEN BY THE MALAYSIAN SIDE

1) To provide adequate personnel to operate the Project.

2) To make necessary arrangements for the provision of local infrastructure and administration of the Project.

5. TECHNICAL COOPERATION

1) The Japanese technical cooperation will be implemented through:

(1) dispatch of the Japanese experts according to the agreement

(2) training of the Malaysian counterpart personnel in Japan

(3) provision of the equipment necessary for the Project.

2) The Project is expected to receive the Japanese experts. The field of experts will be fixed later.

3) Some Malaysian counterparts will be trained in Japan.

4) The Government of Japan will provide equipment and material necessary for the implementation of the Project.

5) The technical cooperation will be conducted for three (3) years. The exact date of its commencement will be fixed later.

PROJECT FOR RESEARCH ON TROPICAL DISEASES IN MALAYSIA 92. 2.

	SUMMARY OF OBJECTIVES/ACTIVITIES	VERIFIABLE INDICATORS	MEANS OF VERIFICATION	IMPORTANT ASSUMPTION
GOAL	contribute to the control of tropical diseases in Malaysia, particularly malaria, dengue and Japanese encephalitis (JE)	·morbidity and mortality of the diseases	·health statistic report in Malaysia	·administrative and reporting system ·financial support
PURPOSE	·upgrading the expertise of molecular biology and biotechnology for: 1. Malaria 2. Dengue and Japanese encephalitis (JE)	1. Malaria ·improvement of the sensitivity and specificity of diagnostic tests for malaria ·publications of research results 2. Dengue and Japanese encephalitis (JE) ·true incidence rates and prevalence of dengue and JE ·strengthening of diagnostic capability at the IMR	·annual report from Ministry of Health (MOH) ·project activity report ·IMR research report	·IMR continuously extends the results to future research projects ·implementation of new technology in clinical fields where appropriate ·close cooperation between IMR and Ministry of Health control programmes
OUTPUT	1. Malaria 1) development and use of DNA probes for malaria diagnosis 2) identification and characterization of protective epitopes of malaria antigens 3) analysis of mitochondrial genes 4) a better understanding of vectorial status of malaria vectors at the molecular level 2. Dengue and Japanese encephalitis (JE) 1) strengthening of diagnostic capability using molecular biology and biotechnology 2) epidemiological studies on dengue and JE 3) understanding of pathogenesis of dengue hemorrhagic fever (DHF) at the molecular level	1. Malaria · sensitivity and specificity of diagnostic tests using DNA probes · identification of protective epitopes · characterization of mitochondrial genes · identification of susceptible/refractory genes of vector mosquitoes 2. Dengue and Japanese encephalitis (JE) ·standard laboratory manual of diagnostic methods on dengue and JE using molecular biology and biotechnology ·records of laboratory results ·manual for specimen collection and shipment ·record of epidemiological data ·comparative nucleotide sequences on various virus strains isolated from 1) severe DHF and mild dengue fever cases 2) mosquitoes ·development of training programmes for laboratory personnels	·project activity report by team leader (quarterly) ·reports of the Japanese experts ·report of Malaysian trainees in Japan ·scientific publications ·report of planning and consulting team in year 1 ·report of advisory team in year 2 ·report of evaluation team in year 3 ·results of tests carried out	·IMR continuously extends the results to future research projects ·close cooperation between IMR and Ministry of Health control programmes ·official clearance of molecular biology experiments where appropriate ·close cooperation between IMR and JICA project team ·support from universities in Japan ·assignment of counterparts and laboratory technicians
INPUT	〈Japanese side〉 1. dispatch of Japanese experts 2. training of Malaysian counterparts in Japan 3. supply of equipments 4. other necessary supplies 〈Malaysian side〉 1. identification of appropriate local counterparts 2. establishment of maintenance / administrative system	〈Japanese side〉 1. Japanese experts long term: 5～6 persons for 3 years short term: less than 8 persons per year 2. counterpart trainees: 3 persons per year 3. equipments: ¥ 100,000,000 (M$ 2 million) for 3 years 〈Malaysian side〉 1. provide sufficient number of local staff 2. contribute to the local cost of consumables	·R/D (record of discussion) ·confirmation of dispatch of experts ·training of Malaysian counterparts in Japan ·supply of equipments	·JICA provides the appropriate allocation in sufficient amounts at the designated time ·sufficient experts from Japan are provided ·Malaysian side provides the necessary support throughout the project ·sufficient Malaysian staff is available throughout the project

7. 資　料

1）ＩMR annual report 1991 より

9.2. BUDGET FOR 1988

In the year under review, IMR's total budget can be summarized as follows:

i)	From the Malaysian Government: For personnel emoluments and operating expenditure.	$ 9,882,930.00
ii)	Training and Scholarship Allowances: For trainees attending the IMR's Senior and Junior courses in Medical Laboratory Technology.	$ 1,390,270.00
iii)	Trust Accounts: USAMRU/SEAMEO-TROPMED/WHO/PORIM	$ 3,440,079.00
iv)	Research and Development Fund:	$ 6,821,207.00
	TOTAL	$21,534,486.79

9.2 BUDGET FOR 1989

In the year under review, IMR's total budget can be summarized as follows:

i)	From the Malaysian Government: For personal emoluments and operating expenditure.	$10,399,675.00
ii)	Training and Scholarship Allowances: For trainees attending the IMR's Senior and Junior courses in Medical Laboratory Technology.	1,286,595.00
iii)	Trust Accounts: USAMRU/SEAMEO-TROPMED/WHO/PORIM	1,320,218.23
iv)	Research and Development Fund:	6,432,500.00
	TOTAL	$19,438,988.23.

8.2 BUDGET FOR 1990

In the year under review, IMR's total budget can be summarized as follows:

i.	From the Malaysian Government:For personal emoluments and operating expenditure	$11,307,000.00
ii.	Training and Scholarship Allowances: For trainees attending the IMR's Senior and Junior courses in Medical Laboratory Technology	1,319,000.00
iii.	Trust Accounts: USAMRU/SEAMEO-TROPMED/ WHO/PORIM	999,293.00
iv.	Research and Development Fund:	3,241,550.00
	TOTAL	$16,866,843.00

DENGUE

One project which was completed in 1990 was the "Evaluation of intervention in the control of Dengue Transmission in Malaysia". Its main objective was to evaluate the effectiveness of conventional intervention methods in dengue control. Three squatter areas in Selayang, Selangor, were selected and socio-demographic and Aedes surveys were conducted. It was found that: (i) natural populations of Aedes aegypti and Aedes albopictus in these areas was very high; (ii) ovitrap surveys appeared to be more sensitive than conventional larval survey techniques; (iii) there was only a slight increased tolerance to temephos in the study area and that it can still be effectively used in larviciding operations; and (iv) large scale ultra-low-volume (ULV) spraying with malathion was the most effective means of controlling Aedes adults in these study areas. To date one publication has resulted from this study. (Programme Co-ordinator: Sinniah M.)

Analysis of nationwide Aedes larval survey in Peninsular Malaysia (1988-1989)

Various factors affecting the breeding of Ae aegypti and Ae albopictus in urban towns are deduced from the survey data. An average of 11.6% of the 7822 households interviewed used temephos (Abate) in potable water and the Aedes larval populations was found to be negatively associated with the extent of temephos usage. Ae aegypti preferred indoor to outdoor container-habitats while in areas where Ae albopictuspredominates, both indoor and outdoor habitats are preferred. Household containers that were partially or completely covered had significantly less breeding of these mosquitoes. It was also determined that both Ae aegypti and Ae albopictus prefer to breed in clear, but not necessarily clean water. (Lee H.L.)

Ovitrap surveys

These surveys were initiated in two study areas i.e. Bukit Botak and Taman Sri Gombak Indah in Selayang. A total of 180 traps were set up indoors and outdoors in Bukit Botak whilst 120 traps were similarly deployed in the other area. The results showed that the predominant mosquito appeared to be Ae albopictus found both indoors and outdoors and Ae aegypti population was much lower. These results are reflective of the suburban environment of the study area in which Ae aegypti has yet to replace Ae albopictus through inter-species competition. Larval surveys were also conducted in these two areas. It is concluded that ovitrap survey was the most sensitive. (Lee H.L.)

MALARIA RESEARCH

Projects under the malaria research programme were in molecular biology of the parasite, epidemiological studies, drug sensitivity patterns of malaria isolates and vector studies.

Malaria surveys were conducted in areas with different intensities of transmission. Various serological assays were used to determine differences in immunological experiences of these communities.

The drug sensitivity pattern of *Plasmodium falciparum* isolates to common antimalarials were monitored with the aim of detecting changes in responses which are important in terms of patient management.

Molecular approaches to the study of the parasite include cloning of local isolates and the production of DNA probes for *P. falciparum*. (Programme Co-ordinator: Mak J.W.)

Production of *Plasmodium falciparum* DNA probes

Genomic DNA was extracted from *in vitro* cultured *Plasmodium falciparum* (Gombak A). Sau3A cleaved DNA of the parasite was ligated into the BamHI site of pBR 322, then transformed into *Escherichia coli* DH5a host cells. Transformed colonies were transferred to nitrocellulose and nylon filters and screened with either ^{32}P-labelled or biotin labelled (Bluegene Kit, BRL) genomic DNA of these parasites.

A total of 2000 colonies were obtained in transformation experiments. When screened with ^{32}P-labelled *P. falciparum* genomic DNA, 26 out of 450 colonies were positive by auto-radiography. With the biotin-labelled probe, another 27 out of 180 colonies screened were found to hybridize with this probe. Seven of these colonies also reacted with biotin-labelled *P. vivax* DNA. These clones will be further probed using labelled human DNA to determine their specificity. (Lim P.K.C. & Ambu S.)

Studies on *Plasmodium falciparum* clones

The objectives of this study were to obtain clones from local isolates of *Plasmodium falciparum* and to determine the extent of heterogeneity of these clones in terms of drug sensitivity, isoenzyme patterns and reactivity to malarial antibodies.

Two local isolates of *P. falciparum* namely, Gombak A and ST230 were used in the study. For the Gombak A isolate, a total of 9 clones were obtained using the limiting dilution method. The drug sensitivity pattern of these 9 clones to three antimalarial drugs (chloroquine, mefloquine and quinine) were determined using the WHO *in vitro* microtest system. All the 9 clones were resistant to chloroquine; 4 clones were sensitive while the other 5 were resistant to mefloquine. For quinine, only 1 out of the 9 clones was sensitive to this antimalarial drug.

A total of 10 isoenzyme systems were studied. No electrophoretic bands were observed with the cloned parasites for 5 of these isoenzymes namely, alcohol dehydrogenase (ADH), hexokinase (HK), isocitrate dehydrogenase (ICD), malate enzyme (ME) and phospho-glucomutase (PGM). The other 5 isoenzymes which were present in the cloned parasites were alpha-glyco-phosphate (AGP), glucose phosphate isomerase (GPI), lactate dehydrogenase (LDH), malate dehydrogenase (MDH) and 6-phosphoglucose dehydrogenase (6-PGD). For the three isoenzymes, AGP, GPI and MDH, only 1 electrophoretic band was observed for the 9 clones. For 6-PGD, 2 variants were observed (6-PGD-1 and 6-PGD-2) among the various clones while for isoenzyme LDH, 3 variants were observed.

For the ST230 isolate, a total of 12 clones were established. Preliminary studies with some of these clones indicated that there were 2 variants for GPI, 3 variants for LDH and 1 for 6-PGD. (Lim P.K.C.)

Seroepidemiological studies in malaria

As reported last year, the objectives of the study were to determine the suitability of the various serological tests for the assessment of the endemicity of malaria and to make recommendations for the standardization of these tests. Various surveys were carried out in different parts of Peninsular Malaysia in late 1989 and the results of some serological assays carried out on the samples collected are reported here.

A malaria survey was carried out from 26 October to 2 November 1989 in Betau, Pahang, which is a known mesoendemic area. The parasite rate was 20.5% in the 610 persons examined. Of the infections, *Plasmodium falciparum*, *P. vivax*, and mixed infections accounted for 79.6%, 15.7% and 4.7% respectively. The geometric mean parasite count (GMC) was 344.30 μl^{-1} and 2.20 μl^{-1} for asexual and sexual parasites respectively. The spleen rate in those aged between 2-9 years was 68.29% (56 out of 82), with a mean spleen size of Hackett's 1.68. The parasite rate in this age group was 29.0% (67 out of 231). With the indirect fluorescent antibody (IFA) assays, the geometric mean titres (GMTs) for the total population were 220.1 ± 5.2 and 1627 ± 5.7 using ring and schizont antigens respectively. Enzyme-linked immunosorbent assay (ELISA) optical density (O.D.) values at 492 nm were 0.51 ± 0.19 and 0.19 ± 0.12 using soluble schizont and intact ring-infected erythrocytes respectively.

A survey carried out in Bt. Lanjan and Sg. Lui areas (hypoendemic) from 25 September to 4 October 1989, gave a malaria positive rate of 1.3% among 697 persons examined. Of the 9 infections, 3 (33.3%) and 6 (66.7%) were due to *P. falciparum* and *P. vivax* respectively. The GMC was 1230.26 μl^{-1} and 1.57 μl^{-1} for asexual and sexual parasites respectively. The spleen rate in those aged 2-9 years was 4.48% (9 out of 201), with the mean spleen size of 1.33. The parasite rate in this age group was 2.73% (7 out of 256). The IFA GMTs for the total population were 2.27 ± 5.08 and 4.76 ± 11.34 using ring and schizont antigens respectively. ELISA values were 0.09 ± 0.14 and 0.03 ± 0.03 using soluble schizont and intact ring-infected erythrocytes respectively.

Another survey was carried out among 901 persons in a non-endemic area in Pondok Tanjong, Taiping, from 21-27 August 1989. The IFA GMTs for the total population were 1.23 ± 2.23 and 1.60 ± 3.54 using ring and schizont antigens respectively. ELISA values were 0.02 ± 0.06 and 0.03 ± 0.03 using soluble schizont and intact ring-infected erythrocytes respectively.

The above findings show that in general, mean antimalarial antibodies as detected by both the IFA and ELISA increased with the endemicity of the area. Schizont antigens appear to be more reactive than ring antigens in both the IFA and ELISA. In the mesoendemic area, there was a positive correlation between these two assays ($r = 0.28$, $t = 5.27$, $P < 0.01$). (Mak J.W. et al.)

Monitoring the *in vitro* drug sensitivity of *Plasmodium falciparum*

In 1990, 72 specimens with *Plasmodium falciparum* were tested for *in vitro* sensitivity against some common antimalarials, using the pre-dosed WHO microtest plates. Of those specimens from Betau, Pahang, which were successfully tested, 17 out of 20 (85.0%) were resistant to chloroquine, with schizont growth occurring in wells with >= 8.0 pmol of the drug. None of the 18 and 20 successfully tested against mefloquine and quinine respectively, was resistant. Of those from Gombak Hospital, 9 out of 12 (75.0%) successfully tested were resistant to chloroquine and all were sensitive to mefloquine and quinine. The only successfully tested specimen from the General Hospital, Kuala Lumpur, was found to be sensitive to all three drugs. These findings are very similar to those in 1989. (Mak J.W. & Noor Rain A.)

Control of malaria using permethrin impregnated bednets

The objective of this study was to determine the impact of permethrin impregnated bednets on malaria occurrence and the vector population in an Orang Asli settlement. The study was carried out in a mesoendemic area in Pos Betau, Pahang. During the first phase of this project between April-December 1990, a knowledge, attitude and practices (KAP) survey on malaria and the use of bednets was conducted in the study area. KAP data including demographic data were collected through a house to house survey using a preceded questionnaire. All households were included and an adult or two members were interviewed from each household. Our surveys showed that the study site has 232 occupied houses with a population of 1458 people. Sixty-two percent of the houses have bednets (new and/or old) and 57% of the population sleep under nets. The results of the KAP study indicated that most households were aware of the benefit of using bednets against mosquito bites but appeared to be less knowledgeable about malaria as an illness caused by mosquito. Most respondents were also relatively ignorant about the breeding habits of the mosquito but knowledge about the fact that the mosquito bites at night was good. It was also found that health education was mainly through direct contact with health personnel and that mass media (like radio) as their source of information was minimal. Entomological observations and malariometric surveys were also conducted during the year. A total of 6,434 mosquitoes were collected, of which 4,893 (76.05%) were *Anopheles maculatus*. The overall infection and infective rate of the malaria parasites in *An. maculatus* was 1.33% (60) and 0.70% (28), respectively. (Chiang G.L., Vythilingam I., Adaikalam J. & Ibrahim M.)

DIVISION OF MEDICAL ENTOMOLOGY

Microbial control agents

Screening and isolation of indigenous microbial control agents

To date, a total of 26 larvicidal isolates of *Bacillus thuringiensis* and 6 isolates of *B. sphaericus* were isolated from various habitats throughout Malaysia. Recently, a *B. sphaericus*-like microbial agent was isolated from soil samples collected from Tasik Bera, Pahang. Initial laboratory bioassays indicated that this isolate was highly active against *Anopheles maculatus* (the major malaria vector in Peninsular Malaysia) and *Culex quinquefasciatus* (a nuisance mosquito) in comparison with other known *B. sphaericus* strains. Unlike other microbial control agents, this isolate was found to produce an antimicrobial-like agent which exhibited antibiotic action against Bacillus, but not *E. coli*. (Lee H.L. & Seleena P.)

Clostridium bifermentans serovar malaysia, a new anaerobic mosquito microbial control agent isolated from soil samples collected from Malacca, was studied in collaboration with the Pasteur Institute, Paris. It was reported that the toxicity of this new control agent was due to the sporulated cells which contained spores, parasporal inclusions and feather-liked appendages. Analysis of the inclusion bodies indicated comparable amino acid contents of *B. thuringiensis* serovar *israelensis* and *B. sphaericus* crystals. Pure toxin isolated by ultracentrifugation on sucrose gradients were highly toxic to mosquito larvae. Safety tests on mice showed absence of toxicity when whole cultures were given by force-feeding, percutaneous application, subcutaneous or intraperitoneal injection. (Pasteur Institute & Lee H.L.)

Pure toxins produced by *Bacillus thuringiensis* H-14 (Bti), *B.t. fukuoka* (Btf) and an engineered *B.t. kurstaki* cloned with Bti toxin gene were purified by Renograffin gradient and bioassayed against indigenous mosquito larvae to determine their toxicity. Pure Bti toxin was highly toxic to *Cx. quinquefasciatus* but moderately toxic to *An. maculatus*. Btf exhibited comparable toxicity to *Ae. aegypti* and *An maculatus*. However, cloned Bti 72 KD polypeptide appeared to be relatively inactive against *Ae. aegypti*. This toxin may be inactivated by the process of lyophilisation. (Sarjeet S., Lee H.L., Seleena P. & Inder Singh, K.)

Fermentation studies

For operational purposes, it is necessary to produce indigenous isolates of *B. thuringiensis* utilizing cheap and locally available wastes through fermentation biotechnology. Preliminary studies in shake-flask containing standard nutrient broth or soya bean waste inoculated with a local strain of *B. thuringiensis* H-14 (IMR-BT-8) indicated that it takes about 37 hours to mature and a further 16 hours for the cells to lyse and release the spore and toxin. The biosynthesis of the toxin was first detected 27 hours after fermentation. In the grated coconut waste, fishmeal and rice bran, the bacteria took 28, 26 and 126 hours respectively to mature. The toxin was harvested from nutrient broth at 55 hours and at 50 hours from soyabean, grated coconut and foshmeal. The toxin could only be harvested 150 hours after inoculation from rice bran. No growth was observed in oil palm waste. In terms of endotoxin and biomass production, fishmeal appears to be the most suitable medium. (Lee H.L. & Seleena P).

Field evaluation of indigenous Bacillus thuringiensis

Sand granule formulation of an indigenous isolate of *Bacillus thuringiensis* H-14 (IMR-BT-8) was evaluated in Selayang, Selangor against *Mansonia* larvae breeding in an unused fish pond. Initial results indicated that the larval population was only affected marginally and continued to pupate, although spore counts of water samples pre- and post-treatment confirmed the presence of IMR-BT-8. Spraying of the area with a commercial B. thuringiensis H-14 formulation showed similar results. It is thus concluded that while *B. thuringiensis* H-14 is known to be toxic against *Mansonia* larvae, the mode of delivery of this bacteria to the larvae needs to be improved, since *Mansonia* larvae usually attach themselves to aquatic plants and are partially hidden in the mud at the bottom of the ponds whereby they are protected from exposure to the bacterial toxin. (Lee H.L. & Seleena P.)

Insecticide studies

Laboratory screening

A new chitin synthesis inhibitor (CSI), flufenoxuron (Cascade) was evaluated against II-III instar larvae of *Culex quinquefasciatus* and *Anopheles maculatus*. Continuous exposure of the larvae to the CSI indicated a EC50 value of 0.00012 mg/l towards *Cx. quinquefasciatus*, while a EC50 value of 0.00027 mg/l was obtained for *Anopheles maculatus*. About 5-40% and 10-16% of the *Cx. quinquefasciatus* and *An. maculatus pupae*, respectively, were deformed when tested at concentrations ranging from 0.00001 to 0.001 mg/l. (Lee H.L. & Salleh H.)

Cyromazine (CGA-72662), also a CSI was tested against the immature stages and adult of *Musca domestica*. Test results indicated that this compound was highly active against young first instar larvae with a EC50 value of 0.1 mg/kg rearing medium. At dosages of >0.4 mg/l, complete larval mortality was achieved. Virgin adults fed with high concentration solutions of cyromazine were not sterilized and continued to oviposit. Ovicidal and pupacidal effects of this compound were also not observed. (Lee H.L. & Salleh H.)

Field-collected adults of *Mansonia uniformis* from Batang Berjuntai, Selangor were bioassayed against a synthetic pyrethroid, lambdacyhalothrin. The results showed a LC50 value of 1.83 mg/sq m and LC90 value of 12.83 mg/sq m thereby showing high toxicity to the mosquito. (Lee H.L. & Salleh H.)

Field evaluations

Based on results of laboratory bioassays, flufenoxuron was field-tested against ground-pool breeding *Anopheles* and *Culex larvae* in Trengganu. Applied at a dosage of 1 mg/sq m, the larval population was suppressed for 9 days, while at 10 mg/ sq m, a control period of 12 days was achieved. Pupation in these test larval populations was completely inhibited. (Lee H.L. & Salleh H.)

An attempt was made to control adults of *Mansonia* in Batang Berjuntai by the use of conventional thermal fogging techniques. Thermal fogging using 5 and 10 g a.i. of lambdacyhalothrin did not appreciably reduce the adult populations. Likewise, fogging with 10 and 100 g a.i. of malathion had little effect. It is concluded that migratory *Mansonia* adults from nearby breeding areas may account for the rapid recovery of the natural populations. (Lee H.L. & Salleh H.)

Two new ultra-low-volume (ULV) aerosol generators were evaluated for the control of *Aedes* in a suburban community in Selayang, Selangor. In these trials, ULV grade (96%) malathion was used at a discharge rate of 50 ml/min to fog the entire area. Air-borne caged laboratory-bred *Ae. aegypti* adults showed 100% mortality 6 hours after exposure. Droplet sampling using magnesium oxide coated glass slides showed satisfactory sizes and densities. It was found that the fog readily penetrated into the houses although doors and windows were closed. This finding is extremely important since in large scale operations, it is usually difficult to ensure doors and windows are open. However, as expected no residual adulticidal or larvicidal effects were observed as determined by ovitrap surveys. ULV fogging is therefore still the most efficient way of *Aedes* control especially in large scale control operations. (Lee H.L., Hishamudin M., Salleh H. & Tham A.S.)

A ULV field trial was carried out using Malathion 96% TG (currently being used for dengue control) and Resigen a pyrethroid against *Ae. aegypti*. Malathion gave 92% mortality outdoors whereas in the living room and the kitchen the mortality was 67% and 40%, respectively. Resigen gave poor mortality rates outdoors as well as indoors. Both insecticides did not show promising larvicidal effects. (Vythilingam I. & Panart I.)

Resistance studies

Non-specific esterases are known to be important detoxification enzymes contributing to the development of insecticide resistance in mosquitoes. Although strains of *Ae. aegypti* larvae in Malaysia have been shown to exhibit varying degree of tolerance to temephos (Abate), no studies were conducted on the possible role of esterases. In this study, the level of esterases in 6 strains of larvae was determined by a rapid colorimetric micro-test. The intensity of the final colour, reflective of esterases level, could be scored visually or scanned by a microplate reader at 450 nm. The resistance ratio was found to correlate significantly with eyescore ($r= 0.92$, $p= 0.001$) while the threshold absorbance value to determine temephos resistance was >0.103. This rapid test can be adopted to screen large samples of field populations to detect the presence of individual mosquito possessing high level of esterases. (Lee H.L. & Salleh H.)

The temephos susceptibility status of field-collected *Ae. albopictus larvae* from Bukit Botak, a dengue study area was investigated in the laboratory. Tests results indicated a LT50 value of 1 91 min in 0.02 mg/l temephos. In comparison, a LT50 value of 209.9 min for a laboratory strain of *Ae. aegypti* was obtained. This shows that temephos can still be used effectively in the study area in anti-*Aedes* operations. (Lee H.L.)

Other studies

Trapping of mosquitoes

A study was carried out to compare the effectiveness of CDC light trap, CO2 baited CDC light trap and CO2 trap in sampling the vectors of Japanese B Encephalitis (JE) in a pig farm. It was found that CO2 baited CDC light trap was efficient in trapping the two major species of JE vectors ie *Culex tritaeniorhynchus* and *Culex gelidus*. (Vythilingam I., Chiang G.L. & Wan Izzuddin)

Electrophoresis studies

Ten gene-enzyme systems comprising fourteen genetic loci were assayed for the Selayang, Petaling Jaya and Melaka populations of *Aedes aegypti* and *Aedes albopictus* which are vectors of dengue(DF) and dengue haemorrhagic fever(DHF). Selayang and Petaling Jaya are two areas where cases of DF/DHF have been reported frequently for the last few years. However, in Batu Berendam, Malacca, where mosquitoes were collected for this study, no cases of DF/DHF had been reported for the last five years. A single locus of Adenylate kinase (AK) was monomorphic and common in both species of Aedes. Three out of the ten gene-enzyme systems which were represented by distinctive electromorphs, coded as PGM, GPD and HK, could be used to separate the two species. A high degree of variability was observed in PGM followed by MDH in both strains of *Ae. albopictus*. The values of genetic similarity and genetic distance among the different strains of the same species obtained in this study were of the rank of geographical populations. The results indicate that they were the same genetically with a high degree of similarity (I=0.946 to 0.997). (Chiang G.L. & Prapluthip E.)

Additive to improve the wash-fastness of permethrin on bednets

The objective of this study was to evaluate the use of local starch (tapioca) for improving the wash-fastness of Permethrin alone, Permethrin and starch in hot water and Permethrin and starch in cold water. The final dosage of Permethrin applied was 0.5 g a.i./m of net and the concentration of starch was 1.75%. Bioassay tests using *Anopheles* mosquitoes showed that there was no significant difference between the various types of treatment. The study indicated that the local starch did not improve the wash-fastness of Permethrin on the cotton nets. (Chiang G.L., Sompong J., Ibrahim M. & Adaikalam J.)

Biting behaviour of Anopheles maculatus in Sabah

A second trip to Sabah was made this year as part of the study on the behaviour and biology of different forms of *An. maculatus* in Malaysia. The man-vector contact and host preference of the *An. maculatus* observed in Sabah were different from that in Peninsular Malaysia. *Anopheles maculatus* in P. Malaysia tends to associate with man more than *An. maculatus* in Sabah. The ratio of mosquitoes biting 2 humans to a cow were 1:70 in Tambunan, Sabah and 1:3 in Pahang, P. Malaysia. Results of blood meal precipitin test revealed that none of the specimens collected in Tambunan and Kota Marudu, Sabah fed on human. However, *An. maculatus* in P. Malaysia exhibited a high human blood index of 0.932. In the 6 nights of 12 hours BLC indoor and outdoor collections, very few mosquitoes were collected. No mosquitoes were collected indoor. All *An. maculatus* were dissected but none had oocysts or sporozoites. The investigation strongly indicated that An. maculatus in Sabah was different from that in P. Malaysia despite their similarity in their morphology. (Chiang G.L.)

DIVISION OF RADIOCHEMISTRY

The research programme in the Division is aimed at (1) producing our own immunoassay reagents for hormones (2) developing and validating assay procedures (3) collaborative studies with clinicians on hormonal changes in health and disease. The outcome of the research projects is intended to facilitate the diagnosis and management of disorders

or diseases affecting the hypothalamic/pituitary/thyroid/adrenal/gonadal axes as well as other endocrine and non-endocrine organs.

Serum growth hormone levels following oral glucose load

Growth hormone (GH) levels during 75 g oral glucose tolerance test (OGTT) in 25 normal adults (12 men and 13 women) and in 8 patients being investigated for acromegaly were measured using an in-house double antibody radioimmunoassay. Nadir GH levels at 2 h post-OGTT in normal subjects ranged from 0.4 to 3.1 mIU/L, the 95% confidence interval being 0.4-1.7mIU/L. Although 2 normal subjects exhibited a small paradoxical increase in GH levels at 2 h post-glucose load, their values remained within the established normal fasting level of <7 mIU/L. The time required for nadir suppression of GH levels was 60 minutes for the majority of the normal subjects while nadir only occurred at 120 minutes for subjects with raised basal fasting GH level. In contrast, acromegalic patients showed elevated GH levels and OGTT failed or only partially suppressed GH secretion. Basal fasting GH levels of 3 acromegalic patients (8.5-23.7mIU/L) were only moderately elevated with values that overlap some normal subjects. However, the specificity of diagnosis of acromegaly is improved with the performance of OGTT whereby there is a separation of GH levels of the patients from normal subjects at 2 h after 75 g glucose load. Therefore, OGTT is required for accurate diagnosis and assessment of treatment of acromegaly patients. (Wan Nazaimoon W.M., Satgunasingam N., Ng M.L. & Khalid B.A.K.)

Epidemiology and laboratory investigation of gestational trophoblastic disease in Malaysia

The objectives of this research were (1) to determine the incidence of hydatidiform mole and choriocarcinoma based on data from some government hospitals, (2) to investigate the risk factors for the disease, and (3) to determine the regression rate of serum ßHCG in patients after evacuation of the mole.

Data on the number of cases of trophoblastic disease for 1990 is pending from several hospitals. Analysis will be carried out as soon as they are available. For the case control study to investigate risk factors for the disease, to date, 76 patients and matched controls for 44 of them have been interviewed. For the determination of regression rates of serum ßHCG, 81 patients have been identified to give blood and urine samples at scheduled intervals. However 16 patients defaulted molar follow-up, 1 patient died and 11 patients had to undergo chemotherapy. The regression rates of serum ßHCG for the remaining 53 patients will be determined once their hormone levels decline to normal. (Kamariah K., Satgunasingam N., Lye M.S., Ng K.Y. & Nik Nasri N.I.)

Ferritin levels in hepatocellular carcinoma

While alpha-fetoprotein (AFP) is a well established and fairly specific marker of primary hepatocellular carcinoma (HCC), it is not always raised in proven cases of the disease. The use of other markers which can act as an adjunct to AFP has been attempted and one of these is serum ferritin.

Malaysia on 10 December.

Ms Soh S.H. attended the "First National Scientific Conference of the Malaysian Federation of Medical Laboratory Technologists" from 1-3 June, Kuala Lumpur and presented a paper entitled "Influence of HLA, age and sex matching on graft survival in renal transplantation from related donors".

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SIXTH MALAYSIA PLAN 1991–1995

Price: $25

PRINTED BY NATIONAL PRINTING DEPARTMENT, KUALA LUMPUR
GHAZALI BIN JANI, K.M.N., A.M.P., P.P.T.,
ACTING DIRECTOR GENERAL, MALAYSIA
1991

CHAPTER XIII

Health

I. INTRODUCTION

13.01 Health is an integral part of socio-economic development. It supports the Government's development efforts in attaining progressive improvements in the health status of the population and productivity of the workforce. During the Fifth Malaysia Plan, health sector programmes were expanded to provide support to the other sectors of the economy.

13.02 The overall thrust of the health sector development programmes during the Fifth Plan was the attainment of *Health For All by the year 2000,* aimed at achieving a standard of health that will enable Malaysians to enjoy a high quality of life. This implies a population capable of working productively and participating actively in the social life of the community in which they live. It also implies a longer expectation of life, a decreasing rate of infant mortality and a diminishing incidence of infectious diseases. Towards this end, the strategies and programmes undertaken included more equitable distribution of efficient health services and facilities, both in the urban and rural areas as well as effective collaboration between health and other health-related programmes.

II. PROGRESS, 1986-90

13.03 Consistent with the need to attain better and more equitable distribution of health services and facilities in both the urban and rural areas, the Government undertook the construction of 33 hospitals, 170 health centres and 464 rural clinics as well as the upgrading of 94 health facilities during the Fifth Plan period. Of these facilities, 97 health centres, 187 rural clinics and two district hospitals were completed while other hospitals and major upgrading works were under various stages of construction. Inspite of these additional facilities, the delivery of health

services was affected by the shortage of doctors and specialists in the public sector, especially in general and district hospitals. In addition, the over-concentration of private doctors and specialists in urban areas further affected the equitable distribution of health services in the country.

Preventive Health Services

13.04 Various preventive and promotive health activities were implemented during the period. They included immunization and vaccination, control of communicable diseases, rural environmental sanitation, applied food and nutrition, occupational health and safety, health education, family development, anti-dadah and road safety programmes.

13.05 The effective implementation of preventive and promotive programmes depended largely on efficient inter-sectoral coordination and collaboration of the relevant agencies in the public and private sectors. Although efforts were made to bring about proper coordination among the relevant agencies in the public sector, the need for a national coordinating body was greatly felt in the implementation of health programmes. Efforts were also made to bring about inter-agency coordination, while studies were undertaken to organize and propose mechanisms for more effective inter-sectoral coordination.

13.06 The Government played a dominant role in the provision of preventive and promotive health programmes. Among these, the rural environmental and sanitation programme provided clean water supply and sanitation facilities for about 212,400 rural households, while the applied food and nutrition programme benefited about 78,000 families. The expanded programme of immunization provided extensive coverage, especially BCG 99.4 per cent, poliomyelitis 83.3 per cent, double and triple antigen 84.1 per cent and measles about 61 per cent of immunizable children in 1990. These had contributed to the reduction in the infant and toddler mortality rates from 16.9 and 1.4 per thousand in 1985 to 13.5 and 1.3 per thousand in 1989, respectively. Immunization for rubella was started in 1987 for eligible women aged 15 to 44 years, and that for hepatitis B, in 1989.

Curative Health Services

13.07 Curative health services were expanded during the Fifth Plan period. The Government undertook the upgrading and renovation programmes for existing general and district hospitals which included

the General Hospitals of Ipoh, Johor Bahru, Kangar, Kuala Lumpur, Kuching, Melaka, Seremban and the District Hospitals of Sungai Petani and Taiping. Existing health centres and rural clinics located in various parts of the country were also upgraded and renovated, thus enabling the improvement of health services in the rural areas. In order to improve diagnostic capabilities, high technology facilities such as computerized tomography and other biomedical equipment, costing $55 million, were acquired for general hospitals. The construction of a modern and sophisticated National Heart Institute, costing about $155 million, was started in 1990 to cope with the increasing incidence of cardiovascular diseases. This Institute will be equipped to perform open-heart surgery and to treat various types of cardiovascular diseases.

13.08 The expansion of health services was given high priority with the provision of basic health care and specialist services in medicine, surgery, paediatrics, obstetrics and gynaecology. The facilities for such services were under construction in District Hospitals such as Kulim, Segamat, Batu Pahat and Kuala Pilah. In addition to the above, 97 health centres, 187 rural clinics and two district hospitals were also completed. Where accessibility was a problem, mobile health and flying doctor services were also provided to the interior and remote parts of the country.

13.09 The Government also introduced programmes to improve the quality and increase the utilization of facilities at health centres and district hospitals to ensure effective delivery of health services to the public. In this regard, refresher courses for the relevant personnel in the management of curative health services were also organized.

13.10 Dental services during the period comprised personal dental care and preventive care components. A total of 254 projects were under construction under the personal dental care programme comprising 22 main dental clinics in towns, one school dental centre, 135 school dental clinics, 86 mobile dental clinics, and ten periodontal units in hospitals. Besides these, personal dental care was also provided through rural health centres of which 170 were completed during the Plan period. At the end of 1990, one main dental clinic, 33 school dental clinics, 34 mobile dental clinics and five periodontal units in hospitals were completed.

13.11 Under the preventive dental services programme, the fluoridation of water supplies and dental health education were implemented. Twenty-eight fluoridation plants were under construction in the Fifth Plan of which 14 were completed. Five out of 28 dental health education units were also completed.

13.12 The pharmaceutical service is an important support service that ensures adequate supply of drugs through appropriate purchasing and local manufacture and the control of quality, efficacy and safety of drugs as well as proper procedures for the importation, management and sale of drugs and pharmaceutical products. During the Fifth Plan, various achievements in this field were made. They included the modernization of stores management and inventory control system at the central and state levels, upgrading of pharmacies in hospitals and the implementation of the integrated medical store system.

Manpower Development

13.13 The delivery of efficient and quality health services depends on the supply of trained health manpower. During the Fifth Plan period, there were 4,229 doctors, 249 specialists and 10,500 nurses in Government medical institutions. Despite this, the public health services faced shortages of manpower which affected the delivery and scope of health services. Many trained personnel gradually retired or left the public service to join the private sector, thus creating 370 vacancies for doctors, 171 for specialists and 400 for nurses in 1990.

13.14 In 1990, the doctor-population ratio for the nation was 1:2,560, below the Fifth Plan target of 1:2,000. In terms of distribution by state, Wilayah Persekutuan Kuala Lumpur and Pulau Pinang had a doctor-population ratio above the Plan target, due to high concentration of doctors in the private sector in the two states. All other states had not achieved the Plan target, as shown in *Table 13-1*. In order to overcome the shortage and the inequitable distribution of doctors amongst states, the Government recruited foreign doctors on contract, increased the intake of medical students in local universities and utilized the services of retired health personnel, while trained and competent medical assistants and nurses were deployed to district hospitals and health centres. In addition, the terms and conditions of service for public sector doctors and specialists were improved. The Government also undertook to improve and increase in-service training for doctors who were then deployed to the various hospitals in the country. Other incentives were also provided, such as free institutional quarters for doctors on call duty, higher specialist allowances and greater post-graduate training opportunities for doctors in the various professional fields.

13.15 These measures coupled with the expansion of preventive and curative health care services and facilities, led to an improvement in health status, as shown in *Table 13-2*. The life expectancy for males improved from 67.9 years in 1985 to 69 years in 1989 while for the females

from 73 to 73.5 years during the same period. The maternal mortality rate was also reduced from 0.37 to 0.3 per thousand while the crude death rate was reduced from 5 to 4.7 per thousand.

Medical Research and Development

13.16 The thrust in medical research and development (R&D) was primarily to conduct applied biomedical research aimed at improving the diagnosis, management and prevention of parasitic, infectious and non-communicable diseases as well as assisting the general and district hospitals in pathological services. Considerable advances were made in research on tropical diseases which contributed towards the prevention and treatment of malaria and dengue. Institutions of higher learning were also encouraged to undertake medical research as part of their science and technology development programmes.

TABLE 13-1

DOCTOR-POPULATION RATIO BY STATE, 1985-90

State	*1985*	*1990*
Johor	1: 4,187	1: 3,145
Kedah	1: 5,516	1: 4,277
Kelantan	1: 6,898	1: 3,764
Melaka	1: 3,012	1: 2,648
Negeri Sembilan	1: 3,353	1: 2,617
Pahang	1: 4,583	1: 3,508
Perak	1: 3,544	1: 2,823
Perlis	1: 3,794	1: 3,400
Pulau Pinang	1: 1,925	1: 1,815
Sabah	1: 6,897	1: 5,082
Sarawak	1: 6,696	1: 5,175
Selangor	1: 3,335	1: 2,280
Terengganu	1: 5,555	1: 4,226
Wilayah Persekutuan Kuala Lumpur	1: 815	1: 721
Malaysia	1: 3,175	1: 2,560

TABLE 13-2

SELECTED INDICATORS OF HEALTH STATUS AND HEALTH SERVICE FACILITIES[1], 1980-90

Indicator	*1980*	*1985*	*1990*[2]
Life Expectancy, in Years[3]			
Male	66.70	67.90	69.00
Female	71.60	73.00	73.50
Infant Mortality Rate (Per 1,000)[3]	19.70	16.95	13.50
Toddler Mortality Rate (Per 1,000)[3]	1.80	1.40	1.30
Maternal Mortality Rate (Per 1,000)[3]	0.60	0.37	0.30
Crude Birth Rate (Per 1,000)	30.90	31.70	27.10
Crude Death Rate (Per 1,000)	5.30	5.00	4.70
Doctors Per 10,000 Population	2.60	3.15	3.76
Dentists Per 10,000 Population	0.50	0.66	0.73
Acute Care Hospital Beds Per 1,000 Population[4]	1.70	1.70	1.50
Health Centres Per 100,000 Rural Population[5]	8.86	8.20	6.05

Notes:

[1] The indicators took into account the usage of facilities by temporary immigrants.

[2] Refers to 1989 figures.

[3] For Peninsular Malaysia only.

[4] Excluding special medical institutions and private hospitals.

[5] The decreasing ratio from 1980 to 1990 is due to population increases and the expansion of outpatient facilities in the district hospitals.

Private Sector Participation

13.17 The improvement in income levels and increasing demand for more services led to the expansion in the number of private hospitals and maternity and nursing homes from 119 in 1983 to 192 in 1990. Most of these private facilities were located in urban areas. In the public sector, the privatization of certain non-clinical services such as laundry, security and maintenance of facilities was undertaken in line with the Government's privatization policy. A feasibility study was undertaken to evaluate the viability of privatizing the management of the National Heart Institute which is under construction.

Management of Health Services

13.18 Efforts were made to further improve the management of health services in order to effect greater quality and equity in the delivery of health services and the implementation of health and health-related development programmes. In view of population increases and changes in the population structure, additional and new demand continued to be made on the supply of quality and equitable health services. Towards this end, studies were implemented to improve resource mobilization and utilization as well as better coordination of health services development and operations.

13.19 Improvements were made to the billing system in general and district hospitals to ensure a more effective collection of user charges. A revised system of user charges was implemented to initiate nominal cost recovery in hospitals and clinics in the country. Computerization was introduced in order to create a more efficient billing system.

13.20 Several studies were conducted to improve the management, utilization, and coordination of health services. A feasibility study on the proposed National Health Security Fund (NHSF) was carried out in the Fifth Plan. The study proposed several organizational options for the NHSF. However, the viability of the proposed options needed to be further reviewed to clarify their financial, economic and social implications. A National Health Plan (NHP) study was undertaken in 1990 to identify and mobilize various health resources in the public and private sectors as well as their efficient and equitable distribution and development. The need for a national coordinating body became evident in the process of implementing health and health-related development programmes. The Government conducted a study on the establishment of a National Health Council as the coordinating body for the development of health and health-related programmes and services in the public and private sectors.

III. PROSPECTS, 1991-95

13.21 The development of the health sector during the Sixth Malaysia Plan will continue to pursue the objective of attaining *Health For All by the year 2000*. The strategies will focus on efforts to further develop, strengthen and maintain an efficient and equitable health services system in order to have a healthy population. The system will also provide quality health care and greater accessibility of health services to the population. In this context, further strengthening of the services at the

district level will continue to be implemented. The ongoing NHP study will provide the basis for improving coordination in health development as well as management of the national health services and resources. Substantial Government allocation, amounting to $2,253 million, will be provided under the Sixth Plan to undertake new as well as complete existing programmes and projects undertaken during the Fifth Plan.

Preventive Health Services

13.22 Efficient preventive health programmes will continue to be undertaken during the period in order to reduce future expenditure on curative care. Occupational health and safety will be strengthened as an important component of the preventive health care programme. The on-going study on occupational health and safety will assist in reviewing policies, regulations and guidelines, coordinating the related programmes as well as identifying further legislative requirements. An Institute for Occupational Health and Safety, costing $15 million, will be constructed under the Sixth Plan.

13.23 The basic components of the environmental and sanitation programme will be expanded, particularly in the rural and squatter areas. Priority will be given to areas with a high prevalence of communicable diseases where potable water supply system is not available or affordable by the population groups concerned. A sum of $63 million will be allocated to provide sanitation for 132,000 households and safe water supply for about 200,000 households.

13.24 Priority will be given to the continuation of the applied food and nutrition programme, directed towards the rural and urban poor. The Government will step up surveillance and enforcement on food quality control to ensure compliance with set standards. The local authorities will also continue to complement the efforts of the Ministry of Health. The Ministry will upgrade the Public Health Institute in Kuala Lumpur and its practical training centres in the various states. An allocation of $10 million will be set aside for the training of health staff, such as medical officers of health and health inspectors.

13.25 The expanded programme of immunization against diseases, such as poliomyelitis, diphtheria, pertussis, tetanus and measles, will be continued with priority to improve the coverage, particularly in remote areas. Efforts will be made to achieve complete coverage in BCG immunization. It is envisaged that three million people will be immunized against rubella and hepatitis B during the Sixth Plan period.

13.26 A major health promotion programme to inculcate a healthy life style in the population will be launched during the Sixth Plan. This programme is designed to reduce the incidence of diseases of affluence, such as diabetes and hypertension. Besides this, improving personal hygiene and life styles through health education will be conducted by the health and health-related agencies as well as the mass media, such as Radio Television Malaysia and the Department of Information.

Curative Health Services

13.27 The physical and non-physical facilities for primary, secondary and tertiary levels of health care will be further improved and expanded in the Sixth Plan. The Government has improved its referral system making it more efficient and effective to ensure that patients receive appropriate care based on need. Measures such as decentralized urban polyclinics and day-care services will be continued in order to maximize the utilization of facilities and services at various levels and to ease congestion, especially at general hospitals.

13.28 In consonance with the aim of more equitable distribution of services, the district health system will be strengthened with the provision of X-ray facilities and the upgrading of laboratory services in health centres and polyclinics. The on-going master plan for the upgrading and rehabilitation of 13 existing general and district hospitals as well as other minor upgrading will be formulated by 1992. A sum of $704 million will be allocated for their construction which is expected to be completed by 1995. The upgrading and rehabilitation programme is in line with the Government's objective of providing basic specialist services in medicine, surgery, paediatrics, obstetrics and gynaecology at various selected district hospitals to meet the growing demand for such services. The expansion of basic specialist services will be supported by the supply of adequate trained manpower through post-graduate training.

13.29 Two of the new district hospitals at Yan and Jitra undertaken during the Fifth Plan are expected to be commissioned in 1991. In addition to upgrading, the construction of new curative facilities, such as the 32 district hospitals and the National Heart Institute, will be completed and commissioned before the end of the Sixth Plan period. An allocation of $1,352 million will be set aside to cater for the construction and the purchase of equipment for such facilities. These facilities are expected to provide an additional 1,000 hospital beds by the end of the Sixth Plan period, including beds for open-heart surgery and treatment of cardiovascular diseases. Studies on the upgrading of National Blood Transfusion Services and Spinal Injury Treatment Services will also be completed during the period.

13.30 The construction of a new district hospital with basic specialist facilities in Labuan will be undertaken to support the development of Labuan as an International Offshore Financial Centre. In order to promote and enhance tourism, the Government has also approved the construction of new district hospitals and the upgrading of health facilities in Cameron Highlands, Pulau Langkawi, Port Dickson and Sri Manjung, costing $153 million.

13.31 In the Sixth Plan, development of dental services will continue to aim at further raising the level of dental health of Malaysians through promotive, preventive, curative and rehabilitative measures. Personal dental care and preventive dental programmes undertaken during the Fifth Plan will be continued. Priority will be accorded to economically disadvantaged population groups to ensure an overall balanced provision of dental care in the country. In this context, efforts will be made to improve accessibility and quality of dental services, particularly in the rural areas. Priority will be given to upgrade the knowledge and professional skills of dental personnel and provide more dental specialist services. Priority will also be accorded to expand school dental health services.

13.32 In the Sixth Plan, quality control to ensure the efficacy and safety of drugs will be strengthened. Towards this end, the National Pharmaceutical Control Laboratory will be upgraded at a cost of $13 million. Priority will also be given to improve storage capacity of medical stores to ensure an efficient drug supply system in the public sector. The pharmaceutical industry has vast potential for development as local manufacturers satisfy only about 25 per cent of the nation's needs. The Government will provide the necessary encouragement for the expansion of local pharmaceutical industry as well as encourage local entrepreneurs and foreign multi-nationals to set up more manufacturing facilities in Malaysia.

Manpower Development

13.33 The Government has set a doctor-population ratio target of 1:1,500 for the year 2000 in order to provide a higher level of care to the population and efforts will be made towards achieving this target. During the Sixth Plan, the Government's training programme is expected to produce 2,000 doctors locally, while about 500 doctors are expected to return from overseas. In order to overcome the current shortage of doctors, retired doctors will continue to reemployed. The Government has approved the setting up of a teaching hospital in Cheras for *Universiti Kebangsaan Malaysia* and has commissioned a feasibility study on the

proposed establishment of a medical complex in *Universiti Islam Antarabangsa*, in order to increase the number of student intake into the faculties of medicine so as to increase the supply of doctors. In addition, the Government will continue to send an increasing number of students to study overseas, and more foreign doctors and specialists will be employed on a contract basis.

13.34 The training capacity in existing schools for nurses under the Ministry of Health will be expanded. During the Sixth Plan, about 5,295 nurses will be trained by the Government. The Government will also consider the possibility of recruiting foreign nurses to supplement local supply. The training of other para-medical personnel will involve about 800 laboratory technologists, 2,100 medical assistants, 250 occupational therapists, 630 pharmaceutical assistants, 250 physiotherapists and 520 public health inspectors. In view of the shortage of about 400 nurses in 1990 and further expansion of Government hospitals, the private sector will be encouraged to increase their training capacities to supplement the public sector efforts. Through contractual arrangements, the Government will continue to encourage private physicians and surgeons to work on a part-time basis and to utilize facilities available at general and district hospitals in order to alleviate the shortage of doctors in the public sector.

Medical Research and Development

13.35 The Institute of Medical Research (IMR) will continue to undertake R&D with the objective of developing applied biomedical research and assisting the general and district hospitals in the country to provide more sophisticated pathological services. About $17 million from the R&D fund for science and technology will be allocated to IMR to undertake innovative biomedical research on various aspects of health and health-related problems under the programme of Intensification of Research on Priority Areas (IRPA). Research on diseases of affluence and health problems related to food quality, tropical diseases, Acquired Immune Deficiency Syndrome (AIDS) and other viral diseases will also be undertaken.

13.36 Further research will be undertaken to facilitate the application of available technology to control food and water-borne diseases, nutritional deficiencies, inappropriate fertility and immunizable diseases. Research on non-communicable diseases caused by hazardous factors, such as smoking, alcohol and pollution, will also be expanded. The institutions of higher learning will also be required to cooperate and

coordinate their research under the IRPA programme. Overall a total of $59.8 million will be provided for R&D activities in the medical and health fields.

Private Sector Participation

13.37 The Government will continue to encourage the private sector to provide health services. However, the growth of the private sector health services has to be coordinated in order to supplement the Government efforts in meeting the demand for health services by the public as well as ensuring equitable distribution of such facilities. The Government will consider the recommendations of the Health Services Financing study to reorientate private medical practice to meet the country's need through an agreed code of conduct and practice so as to maintain a standard quality of services based on available facilities and affordability of the consumers. In situations where Government facilities are not available, the Government would use private facilities if they are found to be cost-effective. The Government will evaluate the viability of privatizing the management and operations of the National Heart Institute, without affecting the accessibility of Government employees and the low-income group to medical treatment. The Government will continue to support the setting up of private medical facilities, such as hospitals and clinics, to cater for those who can afford such services.

Management of Health Services

13.38 The NHP study will be completed in 1992. NHP will include the framework for the mobilization and utilization of health resources in the public and private sectors, manpower development, distribution of health facilities and the upgrading and renovation of existing ones, incentives for private sector relocation to under-served areas and the coordination of the public and private sector programmes. A further review of the NHSF study will be undertaken to ascertain the advantages and disadvantages of the proposed scheme compared with the existing system of financing health care in Malaysia. It is also envisaged that a National Health Council will be established to coordinate policies and programmes in the health sector.

13.39 In order to facilitate an orderly development as well as to effect an equitable distribution of health services and facilities between urban and rural areas, a master plan indicating the nature and location of existing and required levels of health services and facilities for the entire country will be drawn up.

IV. ALLOCATION

13.40 The total development allocation for the health sector during the Sixth Malaysia Plan is about $2,253 million, as shown in *Table 13-3*. This amount is 4.1 per cent of the total Federal Government development allocation for the Sixth Plan period compared to 2.6 per cent under the Fifth Plan.

V. CONCLUSION

13.41 The improvement of health services as well as the well-being of society will continue to be emphasized during the Sixth Plan period. The objective of health services will be to improve the quality of life of all Malaysians through the provision of equitable health and health-related services.

TABLE 13-3

DEVELOPMENT ALLOCATION FOR HEALTH, 1986-95
($ million)

Programme	*5MP*		*6MP*
	Allocation	*Expenditure*	*Allocation*
Patient Care Services			
New Hospitals	319	311	1,352
Upgrading & Renovation	383	371	594
Public Health Services			
Rural Health	191	181	160
Dental Services	6	6	7
Training	12	11	67
Other Health Services	33	31	39
Applied Food and Nutrition	21	10	22
Population	16	10	12
Total	981	931	2,253