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Special Article

Activities Supported by the Special Programme for Research and Training in Tropical Diseases (TDR) in the Western Pacific Region

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The Western Pacific Regional Office serves the most populous and perhaps the most diverse of WHO's six regions (Fig. 1). Total population as of 1991 was 1.5 billion, ranging from China's 1.1 billion to small countries/areas of as few as 5,000 people. Levels of development also range from the pre-eminence of Japan to some of the world's least developed countries. The Region presently includes 35 countries and areas.

The total amount of funds provided by the Special Programme for Research and Training in Tropical Diseases (TDR) since its inception is approximately US$272 million, which was used to support 4706 projects. The Western Pacific Region was the recipient of 8% of the total support, or in monetary terms, received almost US$23.8 million (Fig. 2). The largest share went to the American Region followed by the European and the African Regions.

The principles of research and training have been developed in the two interdependent objectives of TDR. They are (1) to strengthen the research capabilities of the endemic countries and (2) to develop new and improved tools for the control of major tropical diseases.

Twenty nine per cent of the total funds (or almost US$78 million) have been used for activities involving the research capability strengthening. Thirteen per cent or about US$10 million were spent on 213 activities in this Region (Fig. 3).

Fig. 4 shows the breakdown of the funding in the Western Pacific Region per year. This, of course, includes the support for the development of human resources or training in research, which I feel is the most important aspect of this programme.

The locations of the provinces in China where the parasitic institutes have been or are being supported by institution strengthening grants are shown in Fig. 5. In 1989, China had a population of approximately 1,112 million people. Shanghai with 12.3 million people is the most populous among the three existing municipalities. You will note that the five most populous provinces in China are represented here, Sichuan being the largest with 103.2 million. Guangxi has the largest population of the five autonomous zones, but ranks eleventh among the entire provinces and autonomous zones in the country. Just this year, the Research Strengthening Group of TDR agreed to provide long-term support to the Hainan Provincial Institute of Tropical Diseases, located in Hainan Island, just off the southern tip of Guangdong province. This province has been newly-developed (four years ago) with a population of about 6.6

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This article is a special contribution of Dr. A. Shirai which was presented at 27th joint conference on parasitic diseases: Japan-U.S. cooperative medical science program and Research coordination meeting between endemic countries and non-endemic countries on important tropical parasitic diseases, in Maebashi, Gunma Prefecture (Prof. M. Suzuki) on July, 1992.

本稿は，日米医学協力研究会寄生虫疾患専門部会合同会議および文部省国際シンポジウム「重要熱帯寄生虫病に関する流行国と先進国との研究調整会議」の合同開催が群馬県前橋市においてなされた折に発表された世界保健機関西太平洋地域事務局 A. Shirai 博士のもので，特別寄稿として掲載する。

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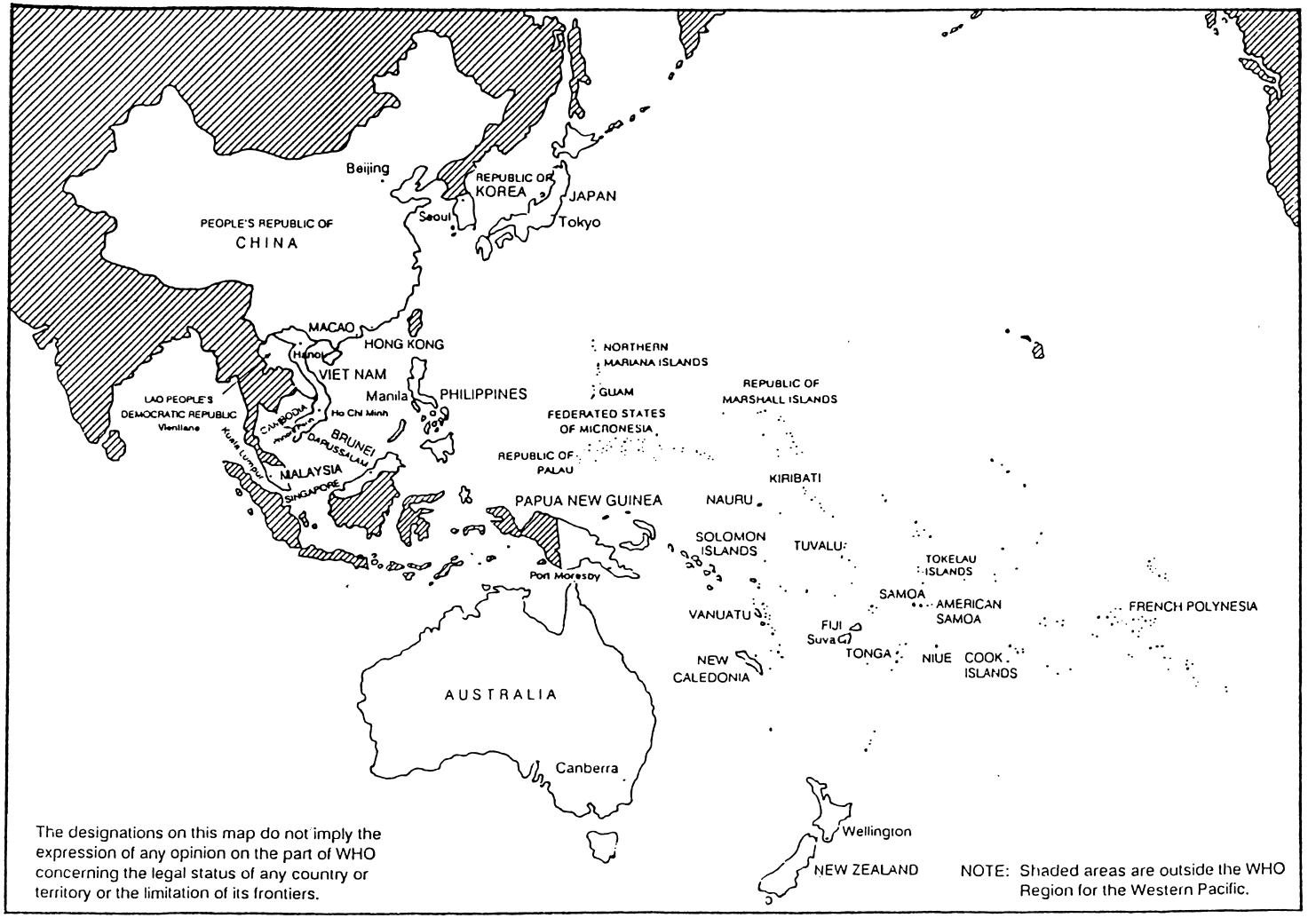

Fig. 1 Map of the WHO region for the Western Pacific.

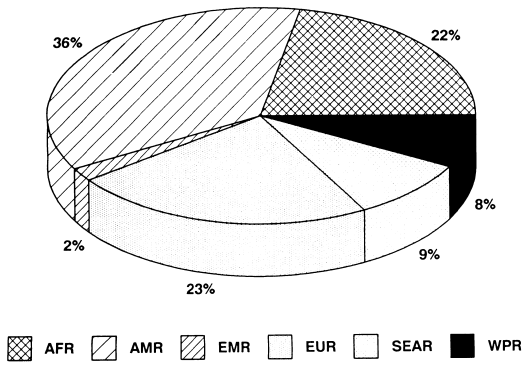

Fig. 2 Total funding of TDR activities (1975–1991).

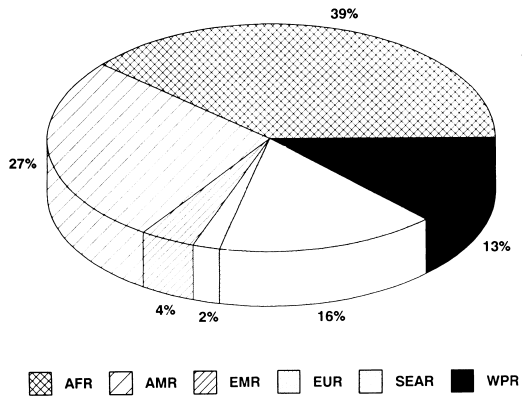

Fig. 3 Total funding of TDR activities research capability strengthening (1975–1991).

million.

The following figures show the provinces in which TDR-supported institutions are located, superimposed on the distribution of diseases of interest to TDR.

The distribution of malaria in China is shown in Fig. 6. Steady progress in its malaria control programme has been observed, with 117,000 reported cases in 1990 as compared to over 3 million in 1978. The majority of the cases were from Yunnan, Hainan, Sichuan and Anhui provinces.

Distribution of falciparum malaria is shown in Fig. 7. The number of *Plasmodium falciparum* cases in China is about 9.1% of total malaria cases, that is about 10,600 cases. The majority of indigenous cases are found in Yunnan and Hainan provinces.

The problem of filariasis has been brought under control in most areas with the exception of Anhui province and its vicinity (Fig. 8). "Under control" means that there is less than 1% of microfilaremic cases – in other words, transmission is arrested. There were about 1 million cases in 1990, including both active and chronic cases.

Schistosomiasis still presents a problem in two principal areas: (1) the lake and swamp regions along the Yangtze river; and (2) the mountainous areas in Sichuan and Yunnan provinces (Fig. 9). One and a half million cases were reported in 1990.

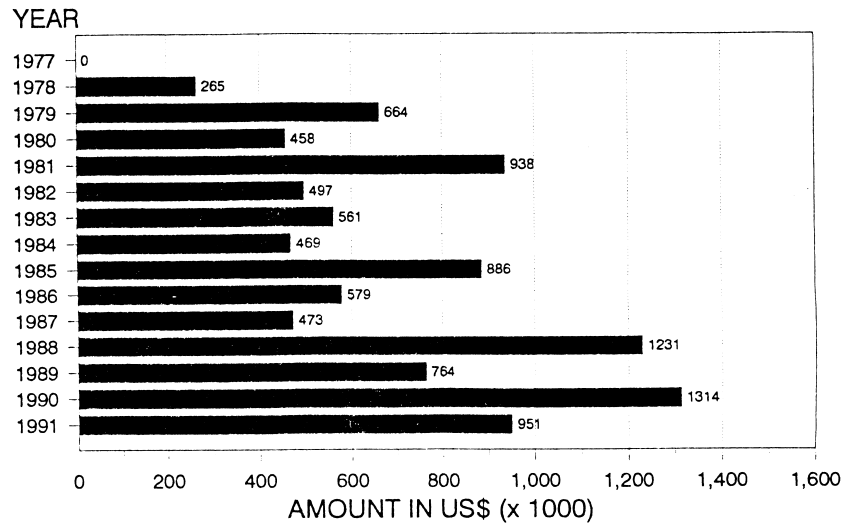

Fig. 4 Funding of TDR activities research capability strengthening.

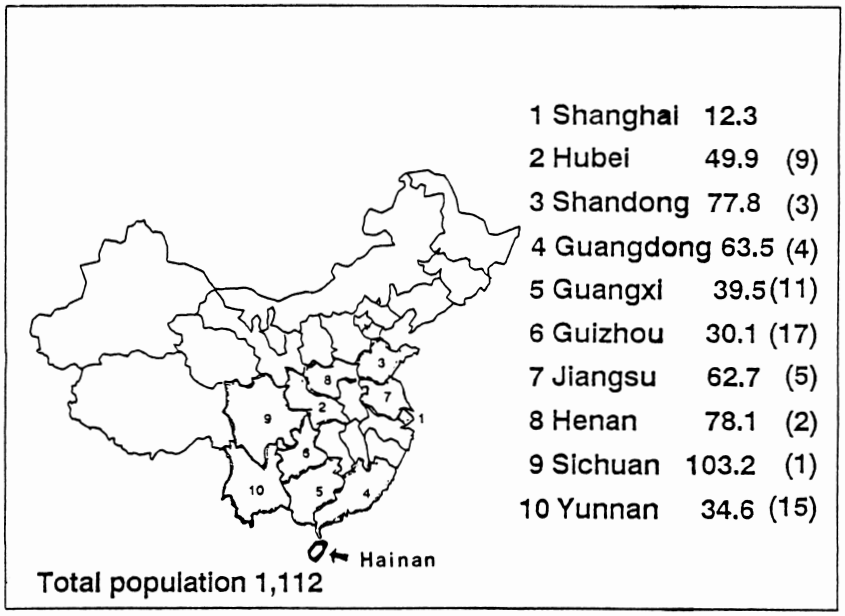

Fig. 5 People's Republic of China population distribution (in Millions).

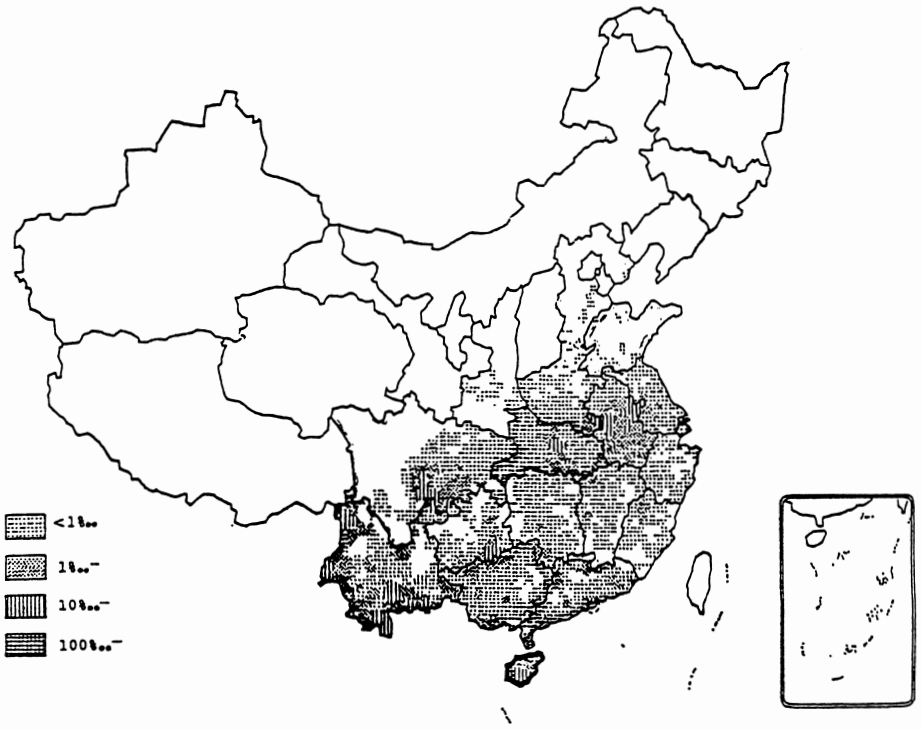

Fig. 6 Malaria in China.

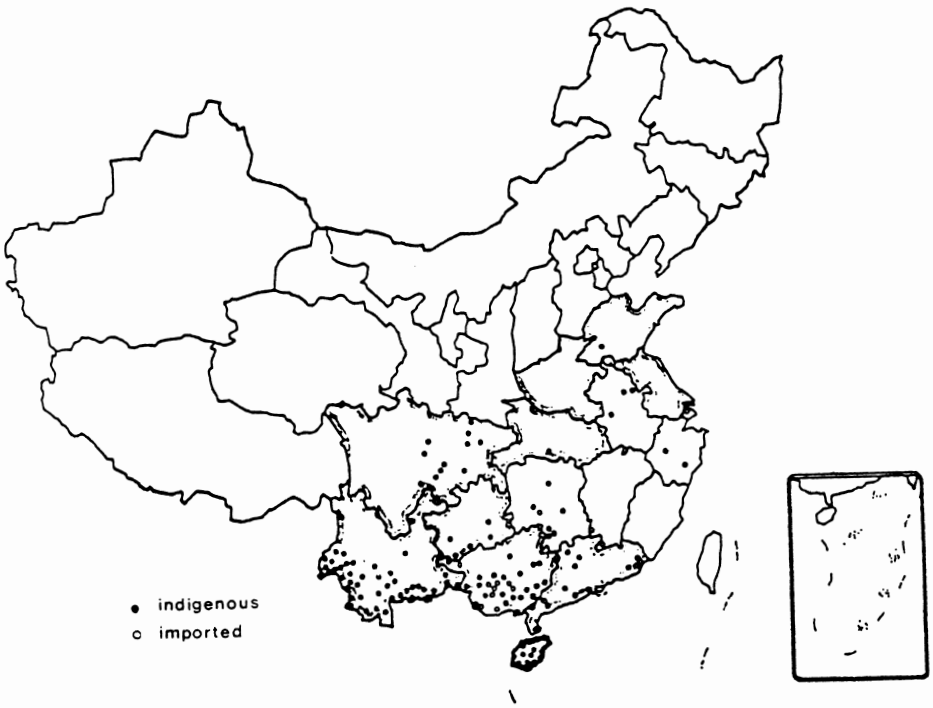

Fig. 7 Falciparum malaria in China.

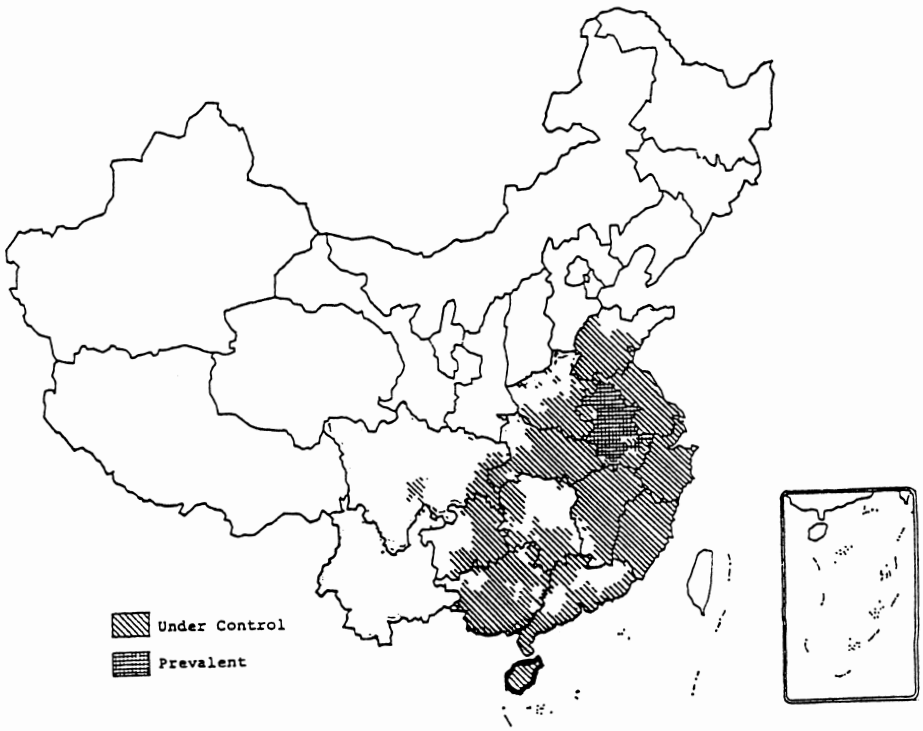

Fig. 8 Filariasis in China.

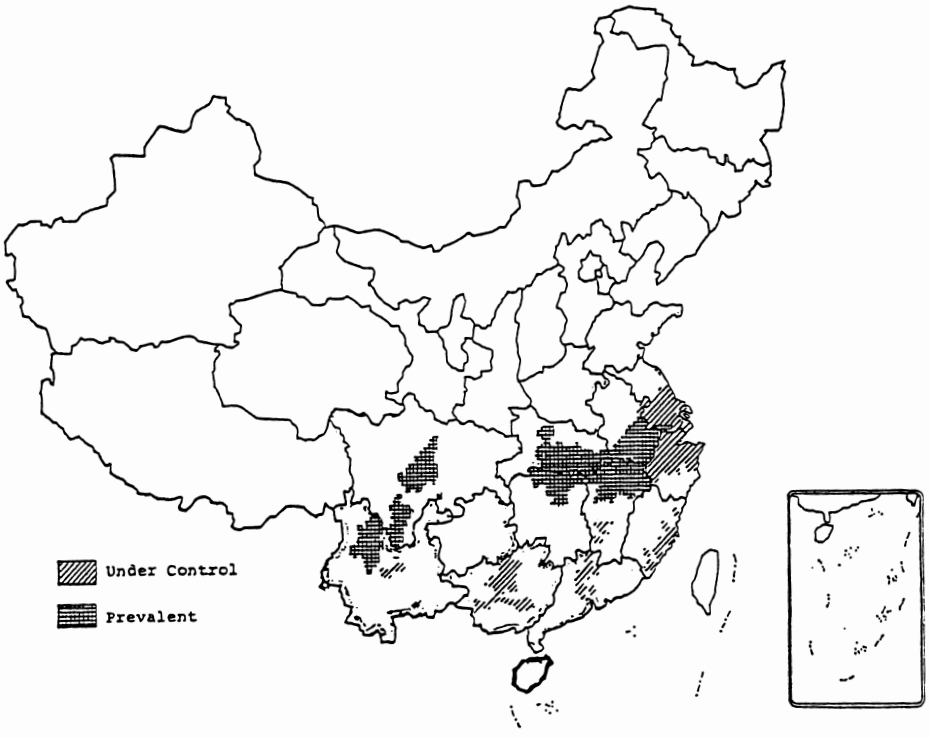

Fig. 9 Schistosomiasis in China.

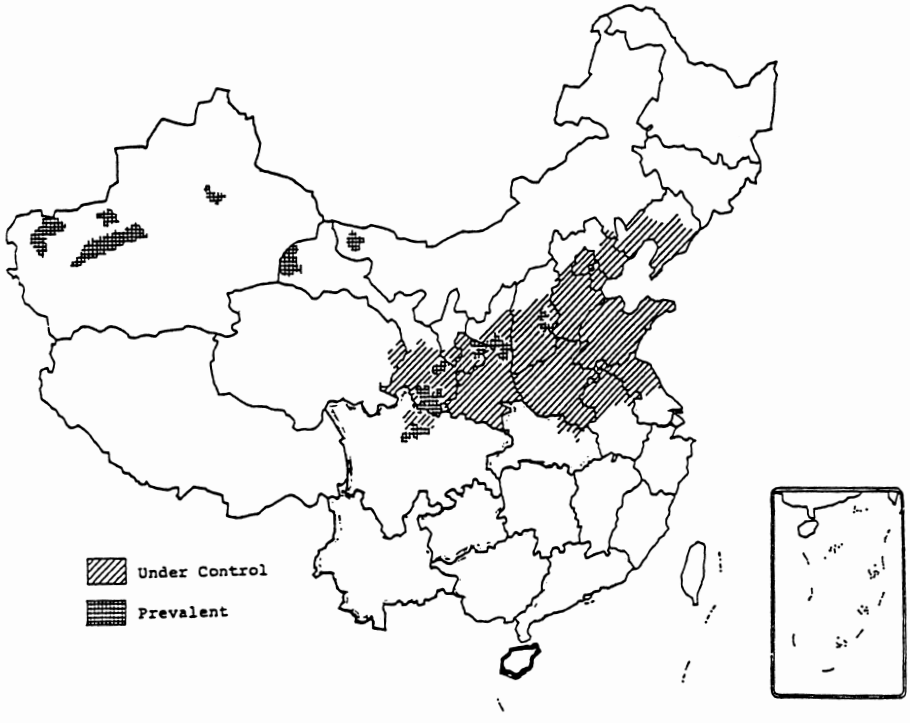

Fig. 10 Kala-azar in China.

There were only 275 reported cases of kala-azar in 1989. Most were found in the mountainous areas of southern Gansu and northern Sichuan provinces (Fig. 10). It occurs sporadically in the desert regions of northern China.

These figures have shown that the TDR-supported institutes are strategically located in places where the diseases are endemic.

In Malaysia, three institutions were strengthened (Fig. 11). One was the Institute for Medical Research (IMR), located in Kuala Lumpur, which is the research arm of the Ministry of Health. TDR support was provided to strengthen capability for field epidemiology and biostatistics, including data processing, immunology, vector control, and biomedical information. It is well-established and one of the leading institutions within this region and has been designated as the WHO Regional Centre for Research and Training in Tropical Diseases and Nutrition.

The School of Biological Sciences, University Science Malaysia, Penang, established with the support of TDR a Vector Control Project with special emphasis on the biological control of medically important insects.

Long-term support was also awarded to the National Drug Research Centre, which is located at the same university. The overall objective was to strengthen and orient the research and training activities towards clinical pharmacological studies in relation to tropical diseases common in Malaysia, namely malaria, filariasis and leprosy.

In Singapore, support was provided to the Department of Social Medicine and Public Health, Faculty of Medicine, National University of Singapore, to establish a MSc degree course in epidemiology and community health.

College of Public Health, University of the Philippines, Manila, was one of the early recipients of TDR support, which was used to strengthen parasitological research capability, especially on immunology of schistosomiasis (Fig. 12). This institution is now considered as one of the leaders in the field of schistosomiasis research.

The College of Social Sciences and Philosophy, also in the University of the Philippines, is comprised of a multi-disciplinary group of social scientists. The principal objective of the project is to

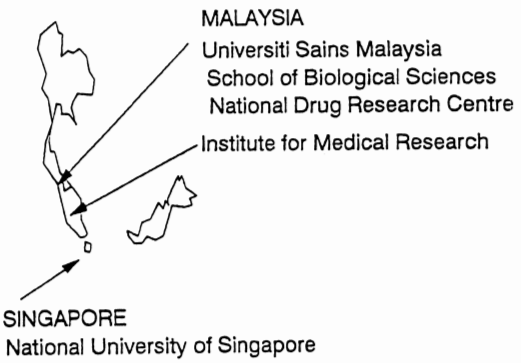

Fig. 11

Fig. 12

intensify and broaden its activities in the area of applied tropical disease research while developing a partnership and a mutually supporting research network with the Department of Health.

The first MSc degree course in health economics in a developing country was established in the School of Economics, University of the Philippines, Diliman.

The Research Institute of Tropical Medicine in Alabang was a recipient of the joint TDR-Rockefeller Foundation grant which will be discussed later.

The support in Viet Nam was provided to the Institute of Malariology, Parasitology and Entomology, Hanoi; its sub-institutes in Ho Chi Minh City and Qui Nhon; and Cho Ray Hospital in Ho Chi Minh City (Fig. 13). The objective was towards strengthening the capability of the institutes to carry out field research, as well as laboratory and clinical research, into such urgent problems as resistant and severe malaria.

Two new institution strengthening grants were recently introduced: a programme-based grant and the joint TDR-Rockefeller Foundation grant.

Programme-based grants were created to help institutions rapidly develop the facilities – including links with other research groups in the same country or region – to conduct productive scientific research related to control of one or more of TDR's target diseases. Of the 16 which were selected for funding, the only programme-based grant in our Region was awarded to Guangxi Institute of Parasitic Diseases Control (Fig. 14). It has established linkages with the WHO Collaborating Centre for Reagent Production at Shanghai Centre for Clinical Laboratory, and the Queensland Institute of Medical Research, Brisbane, Australia. Their study deals with the application of serodiagnostic tests and vector control programmes for sustained malaria control in Guangxi.

Consistent with the need to train scientists through participation in research and with the expectation that a link with a strong research group in an industrialized country can facilitate the scientific "maturation" of and transfer of skills to an institution in a developing country, TDR and the Rockefeller Foundation have arranged to offer grants to two or more research groups or institutions willing to pool their resources in North-South partnerships. Hopefully, these grants should, among other things, help to break the scientific isolation of the "southern" partner and give the "northern" partner a better understanding of field conditions.

Three groups from this Region were successful in receiving this joint support (Fig. 15). The partners of the first group were the Department of Medicine, University of Papua New Guinea, and the School of Medicine, University of Oxford, United Kingdom. The topic of their research was "*P. falciparum* malaria in Melanesia and Polynesia: a study of the pathophysiology and genetic factors involved in individual susceptibility". Unfortunately, this partnership did not work out, so support was terminated.

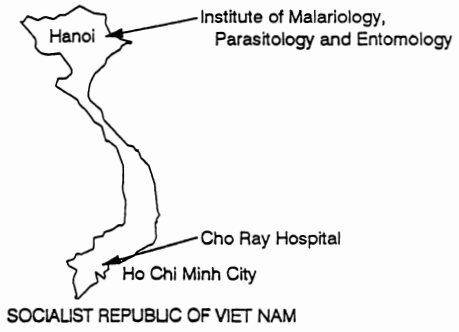

Fig. 13

BY TDR	BY ROCKEFELLER	AREA
University of PNG	School of Medicine, Oxford University	MAL
CPH, University of the Philippines	Walter & Eliza Hall Inst of Med Research	SCH
RITM, Manila	Brown University	
Dept of Epidemiology Shanghai Medical Univ	Harvard School of Public Health, Boston	SCH & FIL
Guizhou Prov'l Inst		

Fig. 15. TDR-Rockefeller grants institutions supported.

INSTITUTES	TITLE
Guangxi Institute of Parasitic Diseases Control Shanghai Centre for Clinical Laboratory Queensland Institute of Medical Research Brisbane, Queensland Australia	Application of Serodiagnostic Tests and Vector Control Programmes for Sustained Malaria Control in Guangxi, China

Fig. 14 Programme-based grant.

The subject of "a multidisciplinary approach to Philippine schistosomiasis" is being undertaken by the College of Public Health, University of the Philippines; Research Institute of Tropical Medicine, Alabang, Philippines; Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia; Queensland Institute of Medical Research, Brisbane, Australia; and the Department of Tropical Geography, Brown University, Providence, Rhode Island, USA.

The group, consisting of the Guizhou Provincial Institute of Parasitic Diseases, Guiyang; Department of Epidemiology, Shanghai Medical University, Shanghai; and Department of Tropical Public Health, Harvard School of Public Health, Boston, Massachusetts, USA; is involved in the study entitled "a China-United States partnership for training and research on schistosomiasis and filariasis".

Career development grants of three to five years were created to provide financial support for research by outstanding developing country scientists. Dr. Wilfred Tiu of the Philippines was one of the three successful candidates from a total of 79 applicants.

The second objective of this Special Programme is to support, through its various Steering Committees, research aimed at developing new methods of preventing, diagnosing and treating the selected diseases. In this case, 71% of the total funds (or approximately US$194 million) were spent towards the research and development activities. The Western Pacific Region received 7% or about US$13 million to support 302 activities (Fig. 16).

The breakdown of the funds received by the year is shown in Fig. 17. It is heartening to note that the amount of funds received have been increasing in the recent years. This is a reflection on the scientists within the Region who are becoming more competitive in seeking funds from international sources.

The following remarks represent only the highlights of the research and development activities

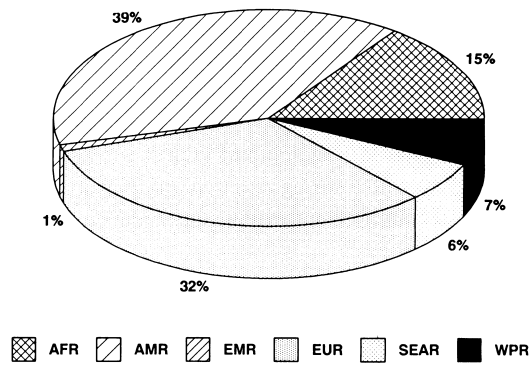

Fig. 16 Total funding of TDR activities research and development (1975–1991).

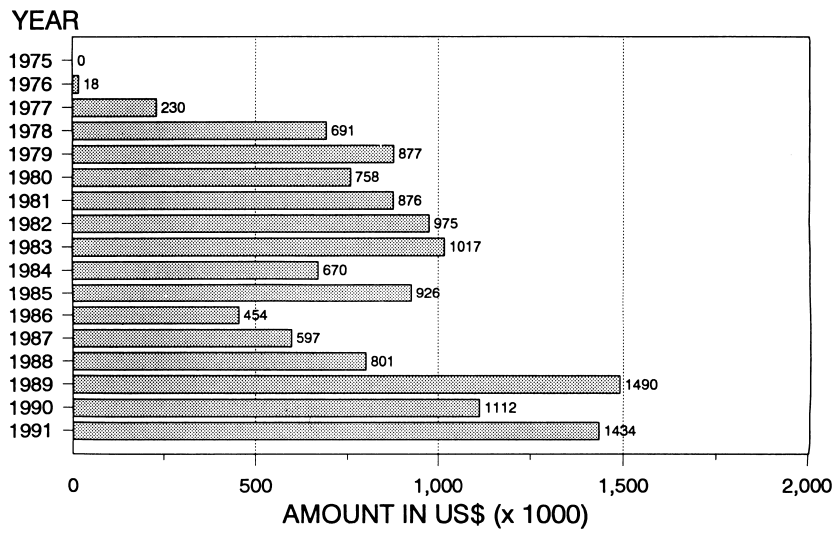

Fig. 17. Funding of TDR activities research and development.

over the past few years within the Western Pacific Region.

MALARIA

In malaria studies, continued efforts are being made to work on new drugs, to optimize existing drugs and to define the factors that impair the use of available drugs (like drug resistance and adverse drug reaction). Much emphasis has been placed on artemisinin and its derivatives. TDR has been working with China in seeking approval and registration of several formulations outside the country and in improving manufacturing conditions. In addition, two comparative studies are under way in Viet Nam in treating severe malaria cases: (1) between artemether and quinine: and (2) between intravenous and intramuscular artesunate. Support was also provided to evaluate pyronaridine and its three analogues *in vitro* against resistant strains and clones of *P. falciparum* obtained globally.

TDR has maintained a very active role in the development of diagnostic tools in malaria with particular emphasis on diagnosis at the most peripheral level of the health services. To this end, tests have been developed for the detection of antimalarial drugs in body fluids by dip stick ELISA and other methods. The dipstick technology is potentially the most sensitive, cheap and simple to use with a detection threshold at the µg/litre level. It is currently being used in South Viet Nam in a comparative clinical trial of quinine and mefloquine. Field evaluations of these test methods are planned in Sabah (East Malaysia) and Peninsular Malaysia for the monitoring of drug use and treatment failure.

A study was undertaken in Japan to establish a new approach to malaria diagnosis using fluorochrome staining. Acridine orange was used to stain the parasites in haemolyzed or non-haemolyzed thick smears. These were directly observed using transmission fluorescence microscopy with any B-excitation filter in light microscope. Combination of filters with simple microscopes using daylight illumination may be a practical diagnostic tool to be used in the endemic countries for parasite detection.

The Malaria Control Service of the Philippines through WHO continue to produce and distribute globally *in vitro* kits for testing the sensitivity of malaria parasites to antimalarial drugs. Available drugs include amodiaquine, chloroquine, mefloquine, pyrimethamine, quinine and sulfadoxine-pyrimethamine. Halofantrine plates are currently being evaluated, while test plates for artemisinin and its derivatives and to pyronaridine are now under development. Low-cost portable incubators, which can be used where a constant temperature is required, are also made and distributed worldwide by this Philippine group.

SCHISTOSOMIASIS

The College of Public Health in the Philippines, in collaboration with the Walter and Eliza Hall Institute of Medical Research in Australia, has shown that fresh eggs mature in lower numbers in chronically egg-sensitized mice. Also the sera from humans with chronic schistosomiasis were capable of decreasing granuloma development by reducing the rate at which eggs mature in the liver. Current research focuses on the hypothesis that egg maturation can be halted by a vaccine curtailing the release of immunopathological egg products, thereby reducing the expression of immunopathological reactions. In addition, the College continues to supply *Schistosoma japonicum* antigens for research through TDR to any interested researchers.

In China, the "collaborative study on immunodiagnosis of schistosomiasis" represents the first full-scale research project on schistosomiasis in China recommended by the Steering Committee. After the addition of two promising techniques for detection of circulating antigens, the results of this project are being prepared for publication.

The rapidly developing interest in ultrasonography has resulted in a study on the application of this technique in a schistosomiasis clinic in Yueyang which is about to be finalized. Two more projects utilizing ultrasonography in the field will soon begin – one in Chengdu, Sichuan, and the other in Nanchang, Jiangxi.

An interesting study is being done in Shanghai Institute of Animal Parasitology where the bovines are being vaccinated against *S. japonicum* with cryopreserved-irradiated schistosomula. This may grow in importance since this parasite is capable of infecting both humans and animals.

FILARIASIS

The main filariasis activities in the Western Pacific Region have involved various clinical trials using ivermectin. Trials carried out in French Polynesia and Malaysia have shown that a single oral dose of 20, 50, 100 or 200 µg/kg clears *Wuchereria bancrofti* microfilaremia in two to three days. However, in the case of *Brugia malayi*, clearance was incomplete (never reaching the 0 level). Side effects were overall mild to moderate and the drug was well tolerated.

Studies comparing a single dose of ivermectin with diethylcarbamazine (DEC), using high, low and split doses, were held in Papua New Guinea.

In China, the Guizhou Provincial Institute of Parasitic Diseases has been involved in a study to determine if ivermectin would be more successful than DEC in clearing microfilaremia from individuals who had already received three or more standard courses of DEC in the previous six to nine months,

Component	A. Samoa	Australia	Cambodia	China	Fiji	F. Poyn.	Hong Kong	Japan	Laos	Malaysia
Malaria		(24) 2,306,930		(21) 734,281				(4) 196,686	(1) 9,190	(14) 384,938
Schistosomiasis		(1) 21,500		(7) 380,469			(1) 45,600	(8) 276,050		
Filariasis	(1) 21,000	(8) 703,594		(1) 98,356	(1) 171,910	(6) 421,923		(2) 141,000		(10) 779,328
Leishmaniasis		(4) 209,290		(4) 79,500				(2) 90,000		
Leprosy		(1) 62,000		(7) 177,300		(3) 78,205		(8) 230,350		(1) 4,800
Biomedical Sciences		(2) 175,730								
Vector Ecology		(5) 234,750		(17) 471,336		(5) 102,200		(1) 32,500		(4) 105,670
Epidemiology & Field Research		(1) 100,000		(2) 19,300						(4) 116,150
Socio-Economic		(2) 55,000			(1) 68,927					(5) 127,010
Training		(1) 31,081	(2) 34,440	(94) 2,190,541						(38) 960,643
Institution Strengthening				(18) 2,402,280						(4) 1,478,000
Director's Initiative fund		(2) 11,380		(11) 94,564						(2) 23,160
Country Total	(1) 21,000	(51) 3,911,255	(2) 34,440	(182) 6,647,927	(2) 240,837	(14) 602,328	(1) 45,600	(25) 966,586	(1) 9,190	(82) 3,979,699

Fig. 18 Summary of TDR-Funded projects in the Western Pacific region by country

but whose microfilaremia had recurred after each treatment (after initially clearing). Both drugs were found to be equally effective in reducing microfilaremia. Therefore, ivermectin was considered to be an acceptable alternative to DEC for use in patients with recurrent microfilaremia.

A large-scale field programme under way in Fiji for the past eight years to assess the effect of various DEC regimens on over 15,000 villagers in five outlying islands has been completed. Single annual doses of 6 mg/kg body weight DEC given to the population at risk over five years is sufficient to bring down microfilarial rates and densities and prevent newer clinical filarial cases and acute episodes. In these areas, microfilarial rates decreased from 6.3% to 0.9% and compared well with standard Fijian scheduled doses (5 mg/kg body weight DEC given weekly for 6 weeks, then monthly for 22 months) where the rates also decreased from 11.6% to 0.7%. Giving this dosage is a good control strat-

New Caled.	New Zeal.	P.N.G.	Phil.	Rep. of Korea	Singa-pore	Sol. Is.	Van.	Viet nam	Component Total
		(12) 576,895	(7) 315,273			(2) 55,088	(1) 4,890	(5) 365,126	(91) 4,949,297
			(7) 461,326	(1) 1,800					(25) 1,186,745
		(3) 132,560	(1) 10,000		(4) 121,700				(37) 2,601,371
	(1) 14,651								(11) 393,441
	(1) 30,000		(9) 361,965	(1) 22,500				(1) 70,000	(32) 1,037,120
					(2) 83,689				(4) 259,419
(1) 21,040	(2) 67,850	(3)	(3) 81,740	(5) 155,500				(1) 38,000	(47) 1,310,586
		(5) 264,535	(1) 27,020		(2) 33,744				(15) 560,749
		(1) 33,340	(13) 538,344						(22) 822,621
			(38) 1,265,911	(1) 20,000	(2) 204,250	(1) 14,800		(17) 302,367	(194) 5,024,033
		(1) 227,282	(6) 772,550					(1) 564,600	(30) 5,444,712
	(1) 9,952	(1) 2,000	(3) 28,500	(3) 26,750				(6) 46,636	(29) 242,942
(1) 21,040	(5) 122,453	(26) 1,236,612	(88) 3,862,629	(11) 226,550	(10) 443,383	(3) 69,888	(1) 4,890	(31) 1,386,729	(537) 23,833,036

and by component as of 23 June 1992 (Number of projects given in brackets)

egy for reducing transmission and morbidity due to the disease.

LEPROSY

One of the major objectives in leprosy research is to study the mechanisms of reactions and nerve damage which lead to deformity. In the Republic of Korea, a study on the characterization of nerve antigens and immunopathogenesis of nerve damages in leprosy patients is underway.

Short-term clinical trials with the fluoroquinolones, pefloxacin and ofloxacin, were successfully concluded in the Philippines among other places – the patients had shown definite clinical improvement and the drugs demonstrated potent bactericidal activity in the mice.

Based on these findings, multicentred field trials have just begun on a new rapid treatment for leprosy patients. The treatment, which is given orally, combines two of the most powerful antibacterial drug available. One is afloxacin, which was originally developed in Japan in 1985. The other is rifampicin, an antibiotic discovered in the 1960s and the mainstay of standard leprosy and tuberculosis therapy. This combination promises to shorten the duration of therapy to only one month, as opposed to the six months to four years required by the standard regimen, known as multidrug therapy. In our Region, the trial is now taking place in the Philippines, while that in Viet Nam will soon begin.They will compare the new regimen with the standard multidrug therapy. Results of the trials, which are double-blind, randomized and controlled, should be available in four or five years.

LEISHMANIASIS

Only a limited amount of research in leishmaniasis has been supported in our Region. These include (1) the invention of anti-leishmania drugs on the basis of the nucleoside structures; (2) the development of sensitive and specific tests to diagnose/assess efficacy of treatment of visceral leishmaniasis with monoclonal antibodies; and (3) the study of mechanisms of immunity against *Leishmania tropica major*: an immunoregulatory basis for vaccine design.

BIOLOGICAL CONTROL OF VECTORS

TDR's objective in the biological control of vectors is to develop new, ecologically more acceptable methods for the control of all vectors of the TDR diseases through the use of natural insect pathogens, parasites and predators. Towards this goal, support has been provided for the local production of *Bacillus thuringiensis H-14* and *B. sphaericus*, for example in China and the Philippines.

There have been studies on other promising agents, such as the nematodes in China and larvivorous fishes (in China and the Republic of Korea). Noted were the advantages of using less harmful, indigenous fish species. In addition, an interesting development has been the stocking of edible fish in rice paddies and small village ponds. Aside from controlling mosquitoes, the food fish provide a significant economic return as a rich source of protein, making the method more attractive to the local communities. This study was done in Guangxi, China.

Collaborative laboratories, such as those in China and Malaysia, are participating in the search, identification and screening of new biocontrol agents. One such organism with good potential for vector control is *Bacillus brevis* which is effective against *Bulinus* snails (China).

SOCIAL AND ECONOMIC RESEARCH

There have not been many social and economic researches undertaken within the Region, with the exception of the Philippines. However, we hope that this situation will be remedied soon as the Social and Economic Research unit, in conjunction with the Research Strengthening Group, has started to organize two- to three-week workshops where biomedical scientists can be introduced to social science research methods on topics related to regional or national needs or to TDR-supported projects in the area. One goal of these workshops is to produce a more informed demand among the biomedical institutions for the participation of social scientists in multidisciplinary research projects. The first of these workshops was held in Shanghai in 1990.

FIELDLINCS

Many control tools and methods have been developed by TDR and are ready for field-testing. However, the lack of social science, epidemiological and operational field-research capacity among

the scientists of endemic countries, constrains the operational testing of these tools. For this reason, the FIELDLINCS programme was established to engage developing country scientists and national control programmes in the design and implementation of appropriate, practical, cost-effective and sustainable control strategies so that greater advances could be made in controlling the diseases within the endemic areas. Towards this end, three protocol development workshops were held in the Region: Philippines, Australia and Shanghai.

The summary of TDR-funded projects in the Western Pacific Region by country and by component is shown in Fig. 18. Relatively little support has been given to Japan; hence, the Japanese scientists should be encouraged to get more involved in priority activities such as molecular entomology and vaccine development, where they are already active.