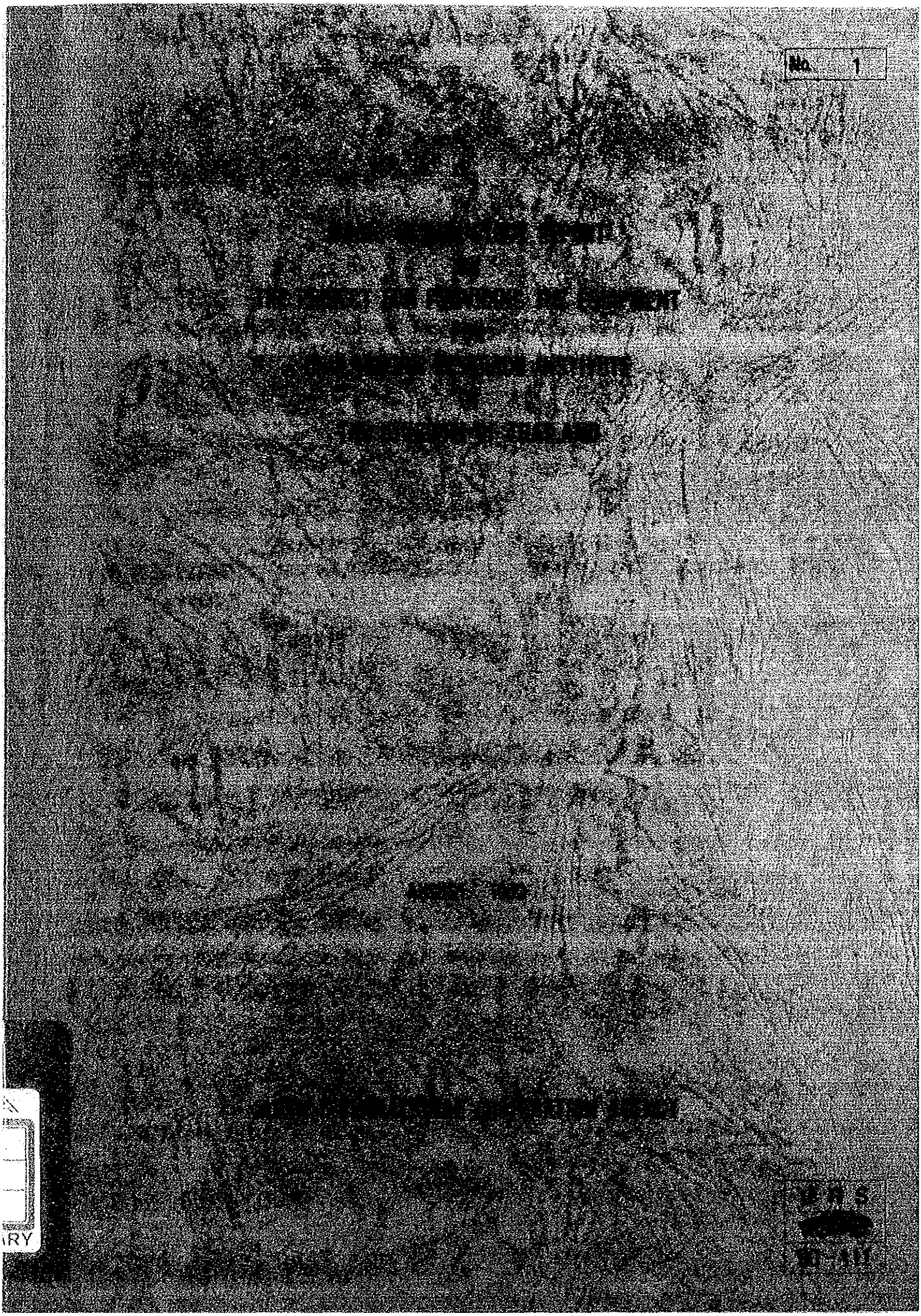


BASIC DESIGN STUDY REPORT
ON
THE PROJECT FOR PROVIDING THE EQUIPMENT
FOR
CHULABHORN RESEARCH INSTITUTE
IN
THE KINGDOM OF THAILAND

AUGUST 1990

JAPAN INTERNATIONAL COOPERATION AGENCY

PREFACE

In response to a request from the Government of the Kingdom of Thailand, the Government of Japan has decided to conduct a Basic Design Study on the Project for Establishment of Bioscience Laboratories in Chulabhorn Research Institute and entrusted the study to the Japan International Cooperation Agency (JICA). JICA sent to Thailand a survey team headed by Mr. Haruo Suzuki, Deputy Management Director of Grant Aid Project Management Department, JICA from April 15 to May 4, 1990.

The Team exchanged views with the officials concerned of the Government of Thailand and conducted a field survey. After the team returned to Japan, further studies were made. Then, a mission was sent to the Thailand in order to discuss the draft report and the present report was prepared.

I hope that this report will serve for the development of the Project and contribute to the promotion of friendly relations between our two countries.

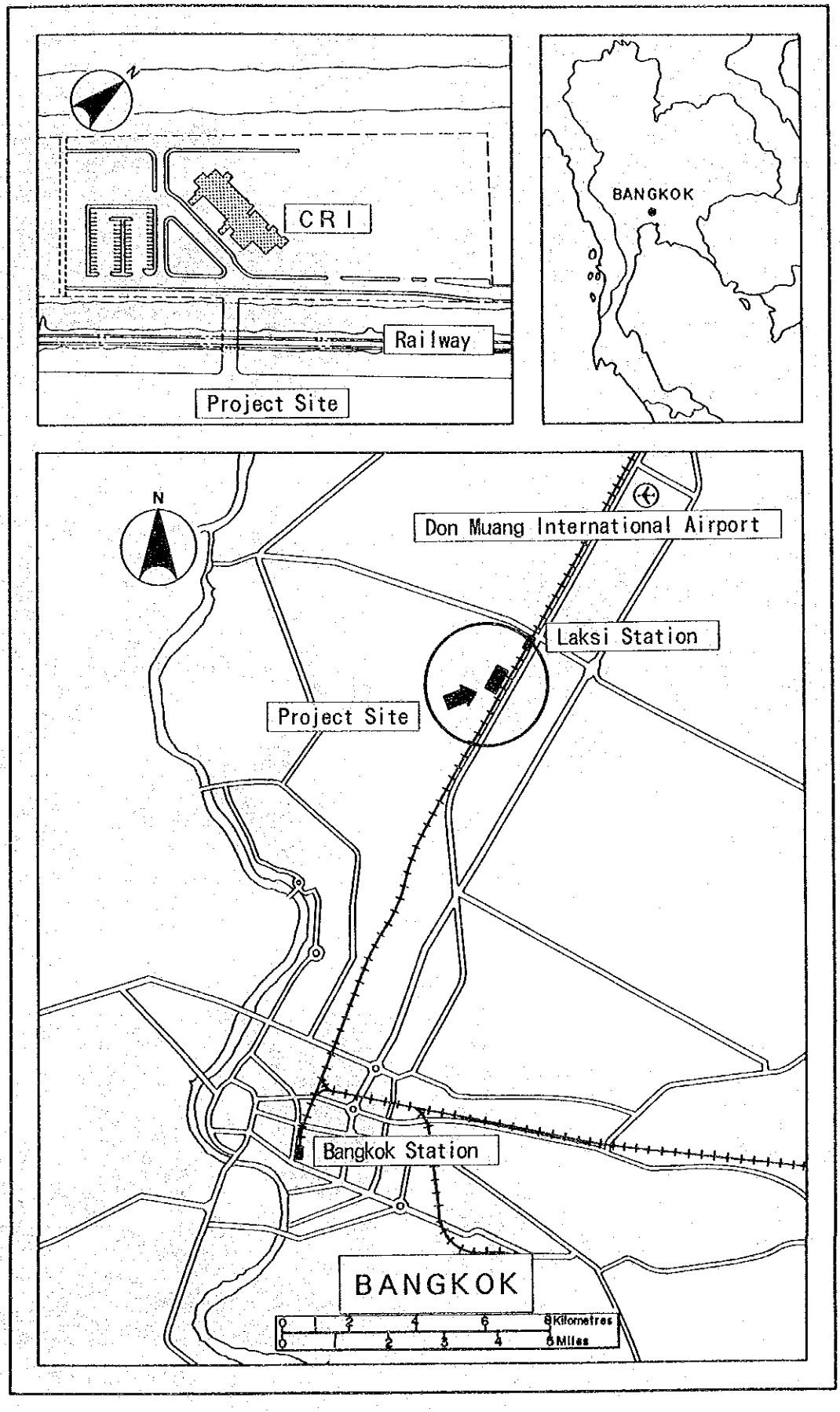
I wish to express my sincere appreciation to the officials concerned of the Government of the Kingdom of Thailand for their close cooperation extended to the teams.

August 1990

Kensuke Yanagiya

Kensuke Yanagiya
President
Japan International Cooperation Agency

PROJECT SITE



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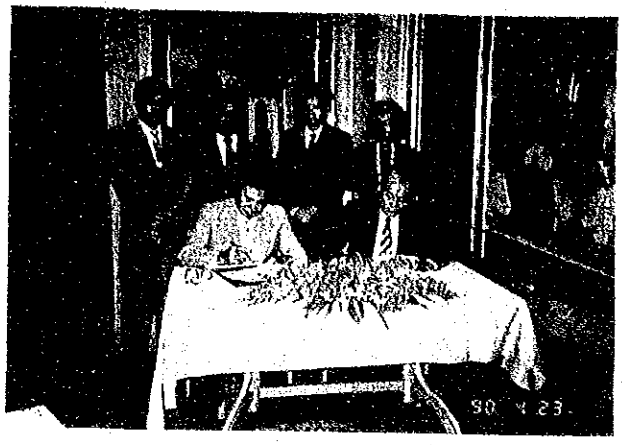


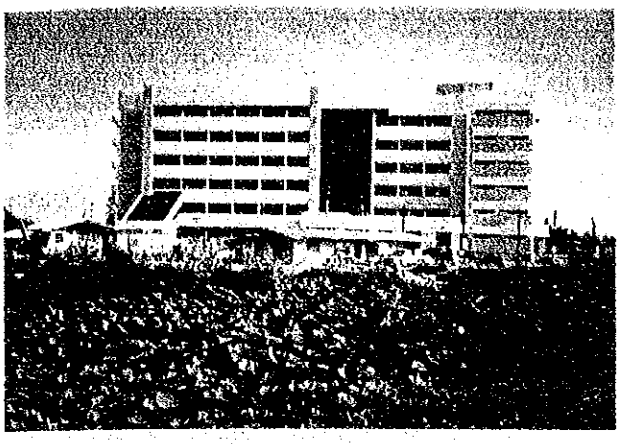
Signing of the Minutes (Basic Design Study)

Meeting at MUA

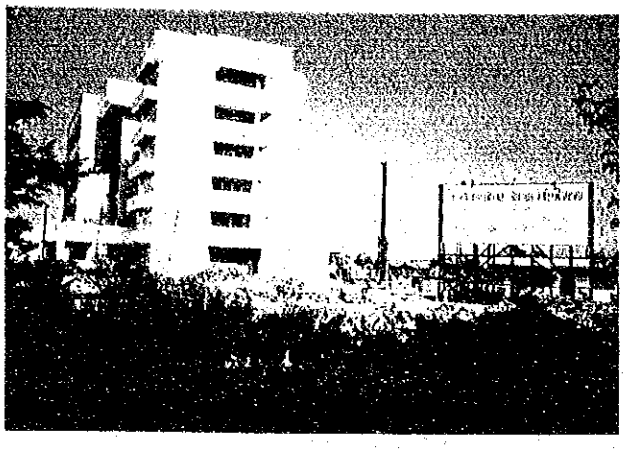
Party after the Signing of the Minutes
(Speech from Dr. Wichit)

Meeting at MUA

Signing of the Minutes (Draft Report Explanation)

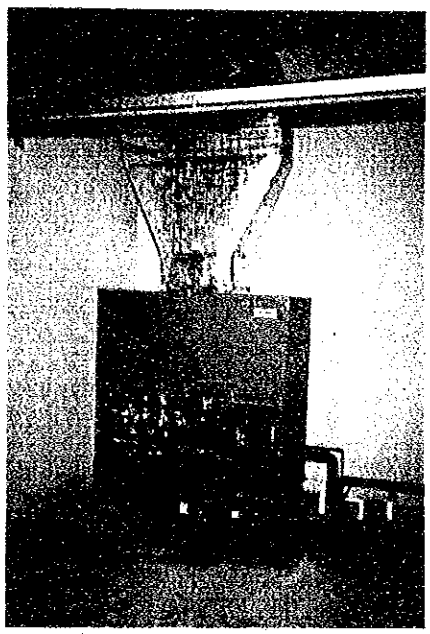


C R I Construction Site



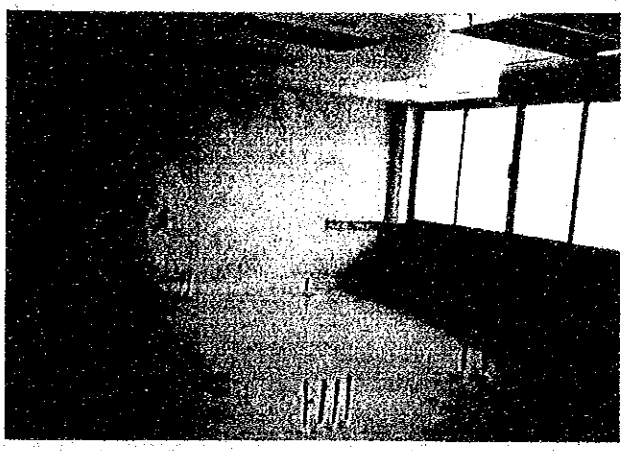
C R I Construction Site

Exhaust Duct for Draft Chamber

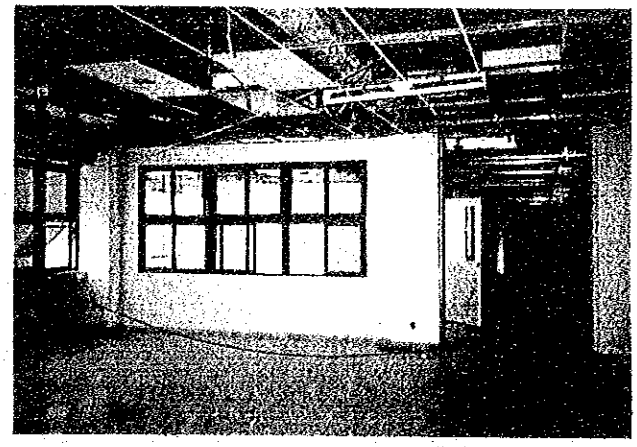


Air-Conditioner

Interior Work (Corridor)



Plumbing Work at Laboratory
(Water Supply & Drainage, Gas, Electric)



Interior Work (Elevater Hall)

SUMMARY

SUMMARY

In Thailand agriculture has been traditionally the center of the industry, forming essential part in the economic and social structure in the country. Farmland, though decreasing every year, occupies 40 percent of the whole land with the forming population of 59 percent of the whole country. It is said that typical six farm products include, first of all rice, and tapioca, sugar cane,tobacco,corn and rubber. Recently however, the yield of new products such as vegetables, fruits, flowers and plants are remarkably increasing.

In 1960's the economy of Thailand started to undergo a drastic change from an agriculture-centered structure to an industry-promoted one aiming at multiplication. Such industrialization of the economy in Thailand has been steadily under way in spite of the stagnation caused by the two times oil crises during the period of 1970's. In 1980's the exports of the industrial products showed a rapid growth as a result of the importation of foreign capital.

In Thailand the national economy has constantly developed owing to the increased foreign investment with the record of 10.5 percent economic growth rate in 1988.

At the same time such rapid economic growth has produced various social problems. One of them the progress of science and technology in the country is unable to overtake such rapid change of the industrial social structure, causing extreme shortage of personnels in this field. Another big problem is that the social and economic gap between the urban and rural area has become wider and wider. In the rural area, where 80 percent of the whole population live, the level of living standard is still very low, producing many problems such as lack of good facilities for health and medical care, deterioration of living environment, poverty, etc.

The Royal Thai Family has been deeply concerned with these problems, and initiated a number of royal projects to improve the "Quality of Life" of the nation. Under these circumstances, Chulabhorn Research Institute (CRI) was established as a general research institute which plays a central leading role in the country.

CRI is a multidisciplinary research institute in the field of science and technology established by Royal Highness Princess Chulabhorn as a director on December 1, 1987. It is operated by the Government budget provided through the Ministry of University Affairs, although the organization is independent of the Government. Besides the Government budget, CRI receives financial support from the Chulabhorn Foundation, which is a private institution set up to support scientific development of the nation, international institutions such as UNDP, and other foreign aids.

As there had been no leading research institute of scientific studies in Thailand, CRI was established as a high priority national project in prospect that it will be a general scientific research institute representing the nation.

The objectives of establishing CRI are as follows;

i) To promote and conduct comprehensive researches of national importance, in particular, those which will improve the "Quality of Life".

ii) To become a center bringing high up caliber personnel in the field of science and technology.

iii) To bring together local and foreign scientists to discuss and solve emerging problems and to promote scientific exchange and become a center for international cooperation in the field of science and technology.

iv) To identify, catalyze and utilize resources for research and development in science and technology.

The activities of CRI are classified into four major areas: Research, Education and Training, Scientific Exchange, and Special Activities.

Research is considered the core activity of the Institute. In the long run, it is planned to cover broad scale of areas including all the fields of science and technology in Thailand. The Thai Government has made requests for grant aid to the Government of Japan and West Germany to be provided with research equipment necessary for making research in the specialized fields. Among research fields of CRI, the request was made to West Germany for providing the equipment in the field of chemical research, while the request to Japan for the equipment in the field of bioscience research.

In response to this request, the Government of Japan made a decision to carry out a basic design study concerning the Project for Providing the

Equipment for Chulabhorn Research Institute in the Kingdom of Thailand (hereinafter called as "the Project"). The Japan International Cooperation Agency (JICA) dispatched to Thailand a basic design study team from April 15, 1990 to May 4, 1990. During this period the study team discussed with the relevant persons of Thai Government and CRI, made a field survey to identify the present situation of the research activities of Thailand, the operating system of the Project, the effect of the Project and the appropriateness of the grant aid, and confirmed the undertakings by the both Governments. After returning to Japan the study team made analysis and an evaluation to perform selection of the most appropriate equipment, cost estimation of the Project, and formulation of the implementation plan. Then JICA dispatched a study team to explain the draft final report of the basic design study of the Project from July 2, 1990 to July 9, 1990.

The research objectives of CRI are making basic subjects aiming at improving public health and medical care in the rural area, utilizing resources effectively, and lifting the level of productivity. As these researches have not yet been undertaken by any university or institution in Thailand, CRI will make an immediate contribution to the improvement of the "Quality of Life" of people in Thailand to meet their fundamental needs as human beings.

The six laboratories and eight research subjects included in the Project are summarized in the following table.

Laboratories and Research Subjects

Laboratories	Research Subjects
Laboratory of Environmental Toxicology	①Influence Studies of Vitamin B Deficiencies on the Mechanisms of Carcinogenesis and Induction of Liver Cancer by Nitrosamines ②Evaluation of Industrial Pollutants or By-products, and Pesticides as Predisposing Factors or Modulators of Physiological and Pathological Status
Laboratory of Biotechnology	③Isolation and Characterization of Microorganisms for Biodegradation of Toxic Industrial and Agricultural Chemicals ④Genetic Manipulation of Aromatic Rice to Produce Disease Resistant Rice
Laboratory of Biochemistry	⑤Plant Carbohydrate Metabolising Enzyme and Their Use for Oligosaccharide Synthesis
Laboratory of Immunology	⑥Development of Immunodiagnostic Methods for Some Unique Tropical Infectious Diseases and Some of Their Complications
Laboratory of Pathobiology	⑦Pathophysiological Study of Hypoxemia in Thalassemia
Laboratory of Pharmacology	⑧Basic Biomedical Research to Support the Improvement of Cerebral Malaria Treatment Regimen

As the eight research subjects included in the request made by the Thai Government are closely related with each other, the collaboration of research works over the bounds of laboratories is necessary. As the method of gene manipulation may be applied in the research subjects 1, 3, 4, and 6 in the above table, these researches could be complementary each other in techniques. The objects of the research subjects 2 and 3 are similar, and their results depend on each other. Biochemical techniques such as cell fractionation method and enzymological method can be shared among research subjects 1, 2, 5, 7, and 8. The object of the research subject 8 is the screening of the medically effective ingredients extracted or synthesized in the chemical laboratories of natural chemistry, medical chemistry and organic chemistry in CRI.

The necessity and appropriateness of each equipment included in the Project are analyzed in relation to the research subjects of CRI. Therefore, an analysis was made to determine if each research proposed by the Thai Government was appropriate as the object of the grant aid

provided by the Japanese Government, and if it corresponds to the goal of the plan prepared by the Thai Government based on the following guideline.

i) The research results could contribute to overcome problems regarding basic human needs in Thailand.
ii) The research results could be applied to solve the specific problems in Thailand.
iii) The researches should not overlap with other researches conducted in other institutes in Thailand.
iv) The researches which have not yet been completed in international scientific society could not be done.
v) The researches should not cause environmental hazards such as pollution and biohazards.

All the eight research subjects proposed by the Thai Government are in line with above mentioned conditions and are judged to be appropriate as the object of the Project. As described above, the content and scope of research work in one laboratory is closely related to another. Therefore, in the basic design a detailed analysis was made in this respect so that an effective and proper equipment project was organized without overlapping. The equipment for the chemical laboratories will be provided by West Germany. Taking this into consideration, the Project was intended to be well-balanced as a whole.

The outline of major equipment provided by the Project is shown in following table.

Outline of Major Equipment

Laboratories	Major Equipment	Number
A. Lab. of Environmental Toxicology	GC-MS, Ultracentrifuge, Gamma Counter, Liquid Scintillation Counter, Lyophilizer, Automated DNA/RNA Extractor, HPLC	23
B. Lab. of Biotechnology	Automated Peptide Sequencer, Automated DNA Sequencer, UV-Visible Spectrophotometer, Ultracentrifuge, High Performance Electrophoresis, Plant Growth Chamber, DNA/Protein Analysis Computer System	29
C. Lab. of Biochemistry	HPLC, Table Top Ultracentrifuge. Fraction Collector, Water Bath Shaker, Ultrapure Water System, Peptide Hydrolysis System, Microscope,	18
D. Lab. of Immunology	Fluorescence Activated Cell-Sorter and Analysis, Automated Peptide Synthesizer, Fluorescence Microscope, CO2 Incubator, Laminar Flow Station, Incubator, Automated Microplate Reader, Automated Cell Harvester	25
E. Lab. of Pathobiology	ESR, Automated Cell Counter, Luminescence Analyzer, Intercellular Calcium Analyzer, HPLC, Impedance Aggregometer	26
F. Lab. of Pharmacology	Organ Bath, Respiratory Mechanical Analyzer, Animal Activity Cage, Spectrofluorometer, Polygraph, Non-invasive Respiratory, Non-invasive Blood Pressure Monitor, Differential pH Meter, UV-Visible Spectrophotometer	21
	Total	142

In the execution of the Project, the consideration between the construction works by the Thai Government and installation works of the equipment by the Project should be taken into account. A sufficient examination should be made in the detailed design stage on the construction works necessary for installation of the equipment, and an efficient coordination should be made with the related institutions so that the construction work undertaken by the Thai Government for additional facilities will be executed according to the original plans.

Undertakings by both Governments are shown in the table below.

Undertakings by Both Governments

Undertaking by Japan Side
(1) Procurement of equipment
(2) Transportation to Thailand and International transportation
(3) Installation of the equipment
(4) Test run, adjustment, training, etc.
Undertaking by Thailand Side
(1) Construction works of a new research building
(2) Electrical works Substation power transmission/trunk line/light/outlet, etc.
(3) Fixtures and furniture
(4) Necessary procedures custom clearance of the equipment
(5) Operation and maintenance cost

The Project will be executed in two separate phases. The basic and general purpose equipment will be provided in Phase I, and the specialized equipment in Phase II. The execution period of Phase I is approximately 7.5 months, and that of Phase II approximately 7.0 months.

The Ministry of University Affairs (MUA) will be responsible for all the works undertaken by Thailand side related to the implementation of the Project, and Foreign Relations Division of the Office of the Permanent Secretary which is substantially in charge of the works will be a section to contact about this Project. Dr. Wichit, Permanent Secretary of MUA, is in charge of CRI as Deputy Director who assists Princess Chulabhorn, Director of CRI.

CRI where the provided equipment is used for its research activities will be responsible for the operation and maintenance of the equipment, administration of the required personnels and budget control. At present the researchers of the science department of Mahidol University where CRI is located are performing actual research works. In the execution of the

Project, these researchers will prepare concrete research plans of the Project.

The budget request concerning the Project of CRI is made from the Office of the Permanent Secretary in the Ministry of University Affairs to the Budget Office, and executed after the approval is given by the Parliament. As this Project is a royal project which is given the highest priority, the disbursements necessary for the operation and planning of CRI are guaranteed.

The Project is to assist CRI to achieve its goal by utilizing the fruit of the research for improving the "Quality of Life" of the nation in Thailand, by providing the research equipment to the bioscience laboratories in CRI and assisting in their effective research activities. The research fields of CRI are subjects to maintain fundamental public life, such as the improvement of public health and medical care for the local farmers, establishment of higher standard of living, advancement of environments, and prevention of pollution. It is expected that the results will make a direct and indirect contribution to the improvement of the public welfare in Thailand.

The objective of CRI, corresponding with the purpose of the present Sixth National Economic and Social Development Project in process now, will be of a help to the well-balanced social and economic development in the country. As its social influence is great, it is judged the implementation of the Project is significant by dint of the grant aid from the Government of Japan.

As for the technical assistance, the Thai Government made a strong request for dispatching Japanese experts. From view point of CRI, the request is considered to be justifiable and to be handled positively.

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APPENDIX

Appendix 1

Appendix 2

1. INTRODUCTION

1. INTRODUCTION

In Thailand the national economy has constantly developed owing to the increased foreign investment with the record of 10.5 percent economic growth rate in 1988. The exports including industrial products have also been expanded. The export of rice has reached the highest amount shown in the past which is approximately 4.8 million tons (about 3.3 million baht). On the other hand, however, there arose economic problems such as expanded trade deficit caused by the increase of imports exceeding exports, and acceleration of inflation.

At the same time such rapid economic growth has produced various social problems. One of them is that the progress of science and technology in the country is unable to overtake such rapid change of the industrial social structure, causing extreme shortage of personnels in this field. Another big problem is that the social and economic gap between the urban and rural areas has become wider and wider. In the rural area, where 80 percent of the whole population live, the level of living standard is still very low, producing many problems such as lack of good facilities for public health and medical care, deterioration of living environment, poverty, etc.

The Royal Thai Family has been deeply concerned with these problems, and initiated a number of royal projects to improve the "Quality of Life" of the nation. Under these circumstances, Chulabhorn Research Institute (CRI) was established as a general research institute which plays a central leading role in the country. The ultimate goal of CRI is to improve the "Quality of Life" of the nation by means of basic and applied research in various fields of science and technology. At present CRI is constructing a building equipped with its own research facilities which is planned to be completed at the end of 1990.

The Thai Government has made a request to the Government of Japan for a grant aid to be provided with specialized equipment required for the research work performed in CRI.

In response to this request, the Government of Japan made a decision to carry out a basic design study concerning the Project for Providing the Equipment for Chulabhorn Research Institute in the Kingdom of Thailand (hereinafter called as "the Project"). The Japanese International Cooperation Agency (JICA) dispatched to Thailand a basic design study team headed by Mr. Haruo Suzuki, Deputy Managing Director of the Grant Aid Management Department of JICA from April 15, 1990 to May 4, 1990. During this period the study team discussed with the relevant persons of the Thai

Government and CRI., made a field survey to identify the present situation of the research activities of Thailand, the operating system of the Project, the effect of the Project and the appropriateness of the grant aid, and confirmed the undertakings by both governments. After returning to Japan the study team made analysis and an evaluation to perform selection of the most appropriate equipment, cost estimation of the Project, and formulation of the implementation plan. Then JICA dispatched a study team to explain the draft final report of the basic design study of the Project headed by Mr. Toru Imamura of the Grant Aid Division of the Economic Cooperation Bureau of the Ministry of Foreign Affairs from July 2, 1990 to July 9, 1990 to make a final discussion of the contents of the basic design study.

This report is the summation of the results of the above described surveys. Members of the study team, the survey itinerary, list of members contacted, and Minutes of Discussions are attached in the APPENDIX 1.1 - 1.4.

2. BACKGROUND OF THE PROJECT

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2.1 Outline of Thailand

2 1.1 Socio-economic Conditions in Thailand

In Thailand agriculture has been traditionally the center of the industry, forming an essential part in the economic and social structure in the country. Farmland, though decreasing every year, occupies 40 percent of the whole land with the farming population of 59 percent of the whole country. It is said that typical six farm products include, first of all rice, and tapioca, sugar cane, tobacco, corn, and rubber. Recently however, the yields of new products such as vegetables, fruits, flowers and plants are remarkably increasing. Rice is still the most important exported item in Thailand, but the trend seems to be changing toward exporting merchandise products with more added values.

The tendency toward industrialization is a strong current in Thailand as well as in the neighboring countries. Agriculture which had long been the first place of GDP was replaced by industry in the latter half of 1980's. In 1987 GDP is 16.9 percent in agriculture and 24.4 percent in industry. The total amount of exported products of agriculture is 34.1 percent, whereas those of industry is 62.7 percent of the whole amount. Nevertheless, the basic structure where agriculture is the basis of the economy in Thailand remains the same so that the development of agriculture has been promoted in a long term plan balanced with industry although it is shaping into the form of agro-industry.

In 1960's the economy of Thailand started to undergo a drastic change from an agriculture-centered structure to an industry-promoted one aiming at multiplication. Such industrialization of the economy in Thailand has been steadily under way in spite of the stagnation caused by the two times oil crises during the period of 1970's. In 1980's the exports of the industrial products showed a rapid growth as a result of the importation of foreign capital. Especially since 1985 textile products have been ranked the first exported item taking the place of rice which had long been in the first place. Such products as television parts, IC products, metal processing products, etc. are also remarkably increasing.

The development of the economy of Thailand is indeed remarkable based on the solid foundation of agriculture and active industrial growth. The growth rate of GDP has been constantly raising with the record of 4.5 percent in 1986, 8.4 percent in 1987, 11.0 percent in 1988 and 10 percent

estimated in 1989. The per capita annual income on the 1988 result was 1,038 US dollar, and is estimated to be 1,190 US dollar in 1990.

The domestic situation, however, has been unable to catch up with this rapid change in the industrial structure, suffering from shortage of qualified personnels required in the fields of research and technological development, marketing, management and planning. As education and training takes a long time, it will be a major issue that should be tackled hereafter by Thailand chasing the neighboring NIES countries.

Various social problems have been raised one after another; i.e. increasing economic difference between rural areas and urban areas like Bangkok, environmental destruction caused by the rapid industrialization and disordered agricultural development, extreme concentration of population into Bangkok which is the center of economy, soaring land price, insufficient infrastructure and public service, concerns of price increase, etc. It is significant for the Government of Thailand to solve these problems.

2.1.2 Related Program

(1) The Sixth National Economic and Social Development Plan (1987-1991)

Since the Thailand Government formulated the 1st national development plan (1961-1965) in 1961, it has continued the 2nd through 5th national economic and social plans. The current plan is the 6th one planned for the period from 1987 to 1991. Because all the previous plans failed to achieve the goal, the current plan aims at the well balanced economic development, focusing on the improvement of the quality rather than the quantity.

The major policy goals of the 6th National Economic and Social Development Plan are as follows.

i) Stabilization of economy and finance.
ii) Development of social and human resources and labor power.
iii) Development of natural resources and environmental control.
iv) Development of science and technology.
v) Review of the government role in the management improvement plan and its development process.
vi) National enterprise development plan.
vii) System development of production, marketing, industrial technology and employment.
viii) Basic service development.

ix) Development of urban and special areas.

x) Development of rural areas.

Since the formulation of the current plan, the economy of Thailand has been achieving outstanding results surpassing the initial target due to the constant foreign investment and activated world economy. In prospect of such economic outcomes as the improvements in employment opportunities, income distribution, and economic balance, the target of this plan was set to be 5 percent average annual economic growth, but it is now well estimated to be 7 percent, much more than the original target. Although there is some difference in the degree of achievement of each goal, generally the economic goals have been achieved as seen in the above described estimation of the economic growth exceeding the target set in the beginning.

On the other hand, such social goals were set as promotion of social development, improvement of the quality of life and reduction of regional differentials. These goals correspond perfectly with the objectives of CRI, indicating that the Project agrees with the aims of the current development plan. It is, however, getting rather difficult to achieve these social goals, not like the steady achievement of the above mentioned economic goals. In fact, negative outcomes have appeared contrary to the initial prospect, such as indiscriminate development in rural areas, environmental pollution, and enlargement of regional gaps caused by industrialization.

(2) Education Policies

Since the National Education Plan was formulated in 1960 in the Thailand, the education has been remarkably spreading and improving. For example, literacy rate increased from 68 percent in 1960 to 90 percent in 1985, and the participation rate also increased considerably. As for the higher educational institutions, the number of national universities and research institutes increased from 9 in 1965 to 16 in 1988, and the number of private universities reached 27 in 1990.

The Government organization having the jurisdiction of education policy is the Ministry of Education. All the educational institutions, except higher education, including preliminary, elementary and secondary schools, vocational training schools and other schools outside the school system are administrated by this Ministry. The aforementioned national and private universities and research institutions are administrated by the Ministry of University Affairs. The National Education Commission

which belongs to the Office of the Prime Minister is in charge of formulating the national education plans and development schemes which are to be basic educational policies.

The educational problems in Thailand are summarized as follows:

i) The participation rate of the secondary education is low compared with other ASEAN countries (30% : the average of ASEAN except Brunei is 51.6%). It is considered to prolong the period of the compulsory education more three years to solve this problem.

ii) The regional gap in educational level is very large. This is caused by the economic gap rather than the different levels of understanding of the importance of education between the people living in urban areas and those in rural areas.

iii) The number of personnels who received higher education is insufficient to meet the demands produced by the development of economy and technology. The low level of quality, as well as the quantity, of the university graduates is also causing a big problem.

(3) Country Aid Research (JICA)

In the Report of Country Aid Research : Thailand (1989) done by JICA, character of the aid to Thailand by Japanese government is determined to assume general, systematic, and flexible so that it may conform to the economic development of the country. The economic growth of Thailand is largely dependent on the development of NIES and other ASEAN countries, but at the same time the prosperity and unity of these neighboring countries/areas is based on the stable growth of Thailand economy. For Thailand which has already achieved a medium level of development, the improvement in research and technology is essential to attain a higher level of achievement.

In this research, required fields of this assistance to Thailand are clarified to be research, mutual interaction of researchers, information exchange of research results and assistance in providing research materials and equipment. It is especially important to strengthen various institutions which could provide with places for the joint research.

In this research the emphasis is also given on the quality of public welfare as the social and economic growth has been achieved in Thailand. It is necessary especially in rural areas to improve public health and medical care, promote assistance in basic medical technology, raise welfare standard in the industries and take effective measure to cope with environmental problem.

CRI is regarded as a leading center of science and technology in Thailand, performing the research works on the improvement of public health and medical standard, basic medical studies in original fields, environmental conservation, etc. aiming at development of the "Quality of Life" in Thailand. These goals of CRI are in conformity with the guidelines of the above described Country Aid Research, and indicating the appropriateness of the Project.

2.2 Chulabhorn Research Institute (CRI)

2.2.1 Outline of CRI

Chulabhorn Research Institute (CRI) is a institute for multidisciplinary research activities established by Her Royal Highness Princess Chulabhorn as a director on December 1, 1987 in honor of His Majesty the King's 60th birthday. Its organization is independent of the Government, although it is operated by the government budget provided through the Ministry of University Affairs. Besides the government budget, CRI receives financial support from the Chulabhorn Foundation, which is a private institution set up to support scientific development of the nation, international institutions such as UNDP, and other foreign aids.

As there had been no leading research institute of scientific studies in Thailand, the Government established CRI as a high priority national project in prospect that it will be a general scientific research institute representing the nation.

The objectives of establishing CRI are as follows;

i) To promote and conduct comprehensive researches of national importance, in particular, those which will improve the "Quality of Life".

ii) To become a center for bringing up high caliber personnel in the field of science and technology.

iii) To bring together local and foreign scientists to discuss and solve emerging problems and to promote scientific exchange and become a center for international cooperation in the field of science and technology.

iv) To identify, catalyze and utilize resources for research and development in science and technology.

2.2.2 Present Status of CRI

At present CRI laboratories are located in the campus of Mahidol University and research works are mainly carried out by the researchers holding adjunct positions (CRI and Mahidol University). CRI has no laboratories and research equipment of its own, but the new building of CRI is now under construction (To be completed in October, 1990), while researches are conducted in the laboratories used by the researchers in charge of each field of study. Located in the faculty of science of Mahidol University, Chulabhorn Research Center is the laboratory where Princess Chulabhorn currently performed the research works.

The activities outside the research fields of CRI are mainly supported by the personal activities of Princess Chulabhorn. As the related institutions of these activity fields are diversified, Princess Chulabhorn, a member of the Royal family, plays an important role in organizing these institutions in order to facilitate the activities smoothly.

2.2.3 Organization of CRI

The organization of CRI is shown in the following chart.

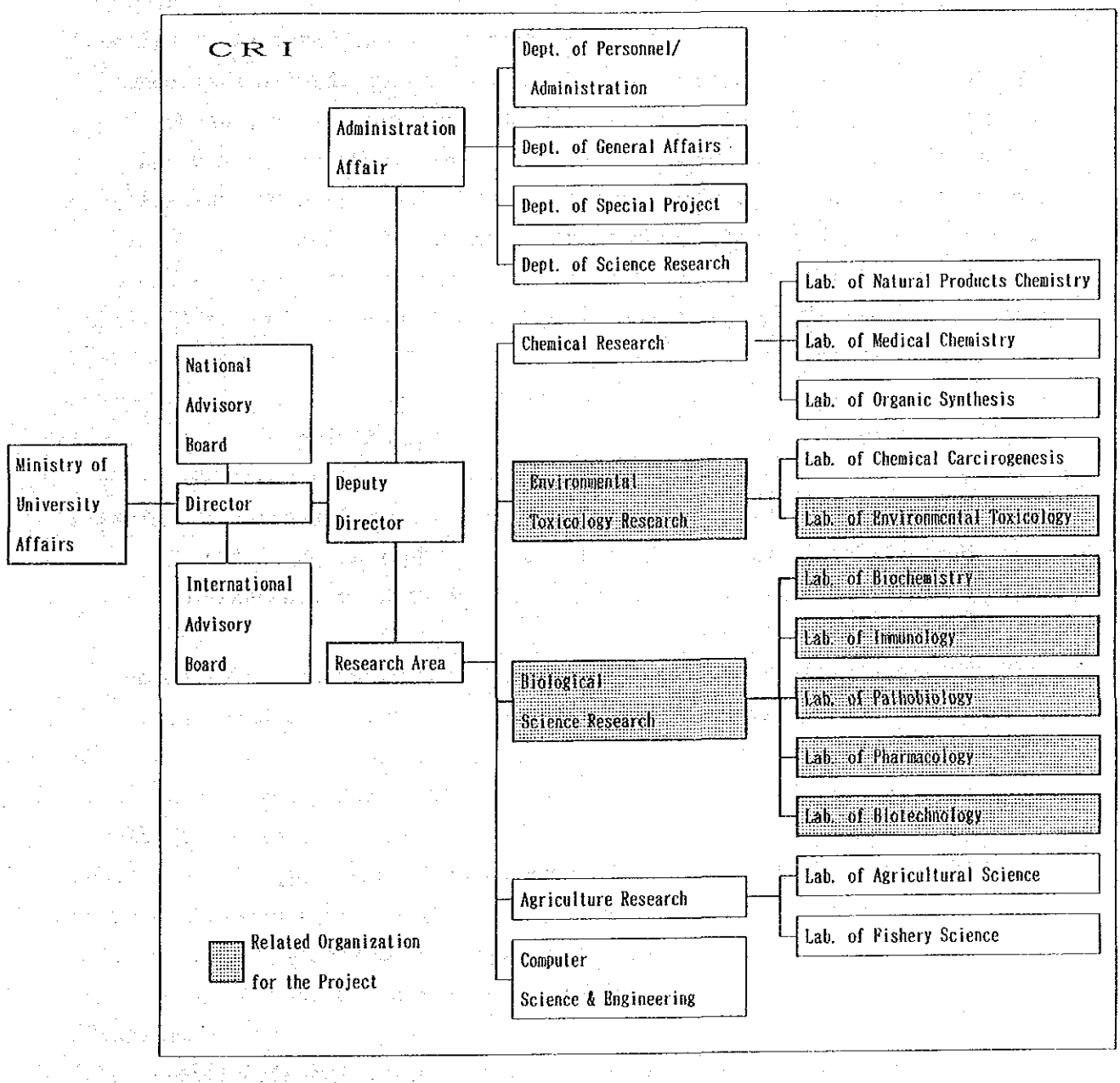


Chart 2.1 Organization Chart of CRI

2.2.4 Activities of CRI

The activities of CRI are classified into four major areas: Research, Education and Training, Scientific Exchange, and Special Activities. the outline of each area is described as follows.

(1) Research

Research is considered the core activity of the Institute. CRI will initiate and conduct fundamental and advanced research with particular emphasis on key major disciplines. In the long run, it is planned to cover a broad scale of areas including all the fields of science and technology in Thailand, which are of national importance but currently priority research is undertaken in the following fields:

Table 2.1 Current Priority Research of CRI

Research	Laboratories
A. Natural Products, Medical Chemistry & Organic Synthesis	1. Laboratory of Natural Products Chemistry 2. Laboratory of Medical Chemistry 3. Laboratory of Organic Synthesis
B. Environmental Toxicology	4. Laboratory of Environmental Toxicology 5. Laboratory of Chemical Carcinogenesis
C. Biotechnology	6. Laboratory of Biotechnology
D. Biomedical Research	7. Laboratory of Biochemistry 8. Laboratory of Immunology 9. Laboratory of Pathobiolgy 10. Laboratory of Pharmacology
E. Agricultural Research	11. Laboratory of Agricultural Science 12. Laboratory of Fishery Science

(2) Education and Training

The development of human resources will be one of the important activities of the Institute. There is an urgent need for qualified

scientists and technologists in Thailand to meet the requirements of economic growth. CRI will organize training courses, seminars, symposia, workshops and conferences to promote exchange of knowledge and information in advanced specialized fields, and to disseminate the scope of research as well as to strengthen national and international cooperation.

<Program>
Princess Chulabhorn Science Congress Program
International Program on Environmental and Industrial Toxicology (funded by UNDP)

(3) Scientific Exchange

CRI will collaborate and maintain contact with scientific institutions and international agencies with the aim to further scientific exchange and international cooperation in matters which correspond to the aims and objectives of the Institute.
<Program>
Exchange Visit by Scientists
Exchange of Information and Data

(4) Special Activities

As a center for national and international cooperation in the field of science and technology, CRI will establish several special programs which are of national and global importance, both in terms of urgency and need, such as the programs to assist the Thai Government in its development efforts. The special programs will seek to utilize the results of CRI's research, education and training activities as well as collaborative association with national and international institutions, to advance the nation's development.

<Program>
AIDS Research Program
Program on Restoration and Development of the Flood-Affected Area in Southern Thailand (funded by UNDP)
Computer Information Service Program

2.2.5 Foreign Aids to CRI

(1) West Germany

The financial aid will be provided from West Germany to the research faculty of CRI as a five-year plan starting from 1990. The contents of the aid include supplying equipment to the four laboratories in the field of chemistry (Natural Product Chemistry, Medical Chemistry, Organic Synthesis, Chemical Carcinogenesis), and dispatch experts. The Project of the Government of Japan include providing equipment for the six laboratories in the field of biotechnology. The equipment of ten laboratories of CRI building which is now under construction will be provided by the financial aids from both Governments of Japan and West Germany. The equipment provided from Japan and West Germany are installed in the different groups of laboratories.

(2) UNDP

1) Program on Restoration and Integrated Development of the Flood-Affected Area in Southern Thailand

The financial aid has been provided from 1989 to 1990 by UNDP to this program in the special activities of CRI with the total amount of US$ 900,000. The contents of the aid cover the costs of construction, equipment, etc. to restore farmlands, aquaculture facilities, public facilities, etc. which were damaged by floods.

2) Research Program on the Environmental and Industrial Toxicology for Industrial Development

The aid plan is to be provided from 1988 to 1991 to this program in the Education/Training of CRI with the total amount of US$ 689,900. The contents of the aid include holding seminars, dispatching experts, and supplying chemicals, glass wares, books, small equipment etc. This program in which some of the laboratories in the research faculty are involved has a strong relationship with the Project. The recipient laboratories are Environmental Toxicology, Biotechnology, Molecular Biology and Immunology, and Pharmacology.

2.3 Ministry of University Affairs (MUA)

The executive agency of this Project is the Ministry of University Affairs (MUA). MUA was formerly the Office of National University which was established under the jurisdiction of the Office of the Prime Minister in 1972 with the purpose of controlling the existing national universities under the administrative institutions in charge of higher education only. In 1982 the Office of State University became Ministry of University Affairs which is to control and supervise the higher educational institutions including national and private universities and graduate schools in the country except elementary and secondary schools controlled by the Ministry of Education. The major duties of MUA are formulation of policies and plans concerning higher education based on the nation's educational plans, standardization of curriculum, personnel administration, budget request and execution. The organization of MUA is composed as follows.

1) Office of the Secretary to the Minister

This office deals with the instructions from the Minister concerning policies and administration. It consists of Policies Division, and Auditing and Administration Division.

2) Office of the Permanent Secretary

This office is substantially a major office in MUA which is to make coordination between government agencies and higher educational institutions such as national and private, universities and institutes. The main duties are project planning, evaluation and administration as to each organization in MUA based on the general scheme that corresponds to the government policies without violating the law. More specifically, the office will review the budget plans prepared by each university to give counsels, and examine such matters as establishment, expansion, transference, incorporation and abolition of universities, departments and divisions. It will also conduct the similar administration over the private universities following Private Higher Educational Institution Act enacted in 1979.

3) National University and Institutes

4) Private Higher Educational Institutions

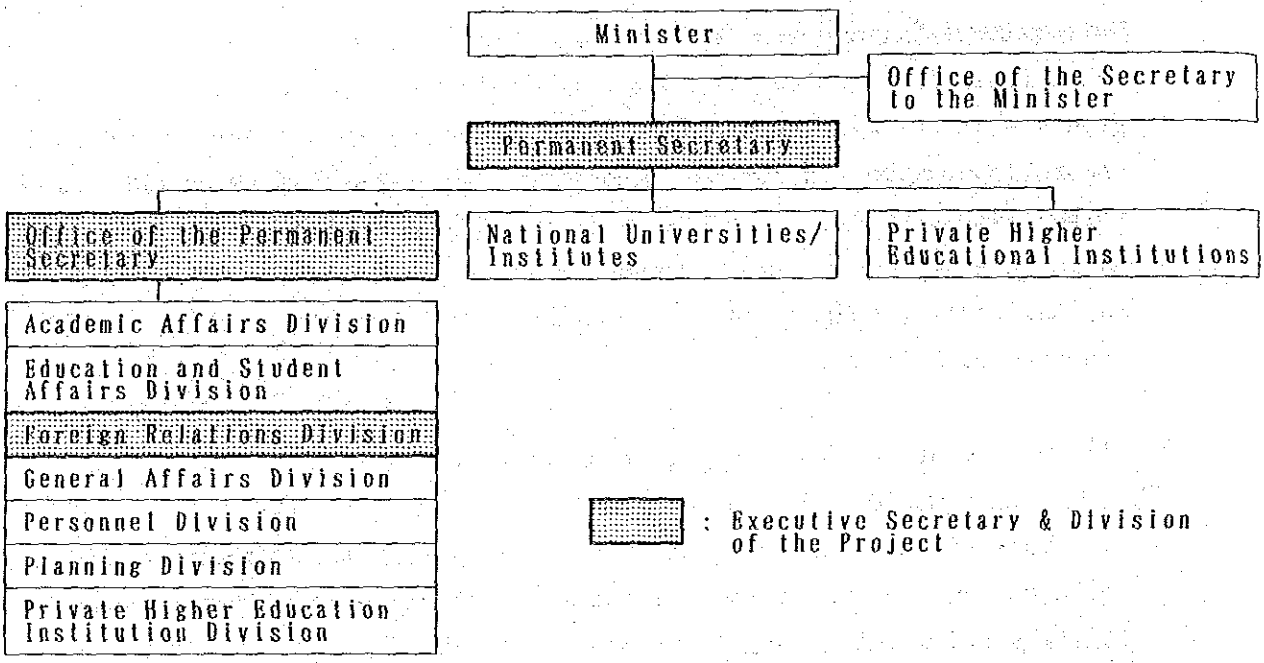


Chart 2.2 MUA Organizational Structure

2.4 Background and Contents of the Request

2.4.1 Background of the Request

In Thailand much efforts have been made in recent years to improve higher education and promote science and technology on the recognition that scientific and technological research is vital to national development. But the need for the advanced technology research has been growing stronger and stronger in various fields as the industrial structure has changed as a result of rapid economic development. Under these conditions of the nation, it is urgently required to establish and fulfill the advanced research institutions.

On the other hand, rural areas, where 80 percent of the whole population live, are considerably underdeveloped so that the level of living standard is still very low, facing many problems such as lack of good facilities for public health and medical care, deterioration of environment, poverty, etc. There had been no institution established with the aim to cope with these diversified problems in the basic public life in a fundamental and comprehensive way.

The Thai Royal Family has made great efforts to improve the "Quality of Life" of the nation. A number of royal projects have been initiated such as agricultural development, improvement of public health and medical care, environmental improvement and preservation, relief aid, etc. with the aim to raise the quality of life of the whole nation by improving living conditions in the rural areas in particular.

Under these circumstances, CRI was established by Princess Chulabhorn in 1987 as a central leading research institute in order to solve these problems. The ultimate goal of CRI is to improve the "Quality of Life" of the nation by means of basic and applied research of science and technology. The research will be of great help to solve the problems in public health and medical care, and improve the environment and public welfare as well as assist the nation in the economic development.

At present CRI is located in the science faculty of Mahidol University. But now the construction work is under way to complete a building equipped with its own research facilities at the total cost of 102 million baht.

The Thai Government has made a request for grant aid to the Government of Japan to be provided with research equipment necessary for making research in specialized fields. The request made to West Germany contains the equipment for chemical research, while the request to Japan

includes the equipment for bioscience research.

2.4.2 Contents of the Request

(1) Contents of Research Subjects Requested in the Project

The Thai Government requested the support of the eight research subjects shown in the following table. As these eight research subjects are closely related with each other, the collaboration of research among the laboratories is necessary. Each subject is unique to Thailand and is in line with the object of establishment of CRI.

The method of gene manipulation may be applied in the research subjects 1, 3, 4, and 6 mentioned in the following table and these research could be complementary each other in techniques. The object of the research 2 and 3 are similar, and their results depend on each other. Biochemical techniques such as cell fractionation method and enzymological method can be shared among research 1, 2, 5, 7, and 8. The purpose of the research 8 is the screening of the medically effective ingredients extracted or synthesized in the chemical laboratories of natural chemistry, medical chemistry, and organic chemistry at CRI.

Table 2.2 Laboratories, Research Subjects and Their Outline Requested in the Project

Laboratories	Research Subjects	Outline of Research
Laboratory of Environmental Toxicology	①Influence Studies of Vitamin B Deficiencies on the Mechanisms of Carcinogenesis and Induction of Liver Cancer by Nitrosamines ②Evaluation of Industrial Pollutants or By-products,and Pesticides as Predisposing Factors or Modulators of Physiolcgical and Pathological Status	Scientific correlation between vitamin B deficiency and hepatic cancer should be studied through laboratory experiments with model animals to decrease the incident rates. Original safety regulation and standard for industrial chemicals and pesticides in Thailand to protect not only nature but also people should be established through laboratory studies with experimental animals.
Laboratory of Biotechnology	③Isolation and Characterization of Microorganisms for Biodegradation of Toxic Industrial and Agricultural Chemicals ④Genetic Manipulation of Aromatic Rice to Produce Disease Resistant Rice	New microorganisms should be isolated and developed for biodegradation of toxic materials such as industrial waste and pesticides by genetic engineering methods to improve envionmental condition. Disease resistent strain of aromatic rice should be developed by biotechnology to enhance the yield of rice.
Laboratory of Biochemistry	⑤Plant Carbohydrate Metabolising Enzyme and Their Use for Oligosaccharide Synthesis	Enzymatic synthesis of oligosaccharides produced from monosaccherides obtained from several crops should be studied for medical use and food addivies.
Laboratory of Immunology	⑥Development of Immunodiagnostic Methods for Some Unique Tropical Infectious Diseases and Some of Their Complications	Quick specific , sensitive, and inexpensive, diagnostic methods with monoclonal antibodies should be developed for several diseases such as Pseudomonas, liver fluke, and parasite infection and bile duct and gall blader cancer to diagnose in early stage and to reduce mortality.
Laboratory of Pathobiology	⑦Pathophysiological Study of Hypoxemia in Thalassemia	Studies on process and mechanism of thalassemia which is one of dominant inheritance disease should be clarified to find effective therapeutic method to release pain and to prolong life soan of patients.
Laboratory of Pharmacology	⑧Basic Biomedical Research to Support the Improvement of Cerebral Malaria Treatment Regimen	Antimalarial activity of newly found chemicals and synthesized drugs should be examined with experimental animals to save human life and reduce number of patient of drug resistant malaria.

(2) Major requested research equipment

The major requested research equipment is shown in the following table.

Table 2.3 Major Requested Equipment

Laboratories	Major Requested Research Equipment
A. Lab. of Environmental Toxicology	GC-MS, Ultracentrifuge, Gamma Counter, Liquid Scintillation Counter, Lyophilizer, Automated DNA/RNA Extractor, HPLC
B. Lab. of Biotechnology	Automated Peptide Sequencer, Automated DNA Sequencer, UV-Visible Spectrophotometer, Ultracentrifuge, High Performance Electrophoresis, Plant Growth Chamber, DNA/Protein Analysis Computer System
C. Lab. of Biochemistry	HPLC, Table Top Ultracentrifuge. Fraction Collection, Water Bath Shaker, Ultrapure Water System, Peptide Hydrolysis System, Microscope,
D. Lab. of Immunology	Fluorescence Activated Cell-Sorter and Analysis, Automated Peptide Synthesizer, Fluorescence Microscope, CO2 Incubator, Laminar Flow Station, Incubator, Automated Microplate Reader, Automated Cell Harvester
E. Lab. of Pathobilogy	ESR, Automated Cell Counter, Luminescence Analyzer, Intercellular Calcium Analyzer, HPLC, Impedance Aggregometer
F. Lab. of Pharmacology	Organ Bath, Respiratory Mechanical Analyzer, Animal Activity Cage, Spectrofluorometer, Polygraph, Non-invasive Respiratory, Non-invasive Blood Pressure Monitor, Differential pH Meter, UV-Visible Spectrophotometer

3. CONTENTS OF THE PROJECT

3. CONTENTS OF THE PROJECT

3.1 Goal of the Project

The goal of the Project is to provide the research equipment required for six bioscience laboratories in the new CRI building. The Project will strengthen the research activities of CRI; and thereby promote improvement of basic human life in Thailand.

3.2 Analysis of the Contents of the Project

3.2.1 Condition of Analysis

The necessity and appropriateness of each equipment included in the Project is analyzed in relation to the research subjects of CRI. Therefore, an analysis was made to determine if each research subject proposed by the Thai Government was appropriate as the object of the grant aid provided by the Japanese Government, and if it corresponds to the goal of the Project prepared by the Thai Government based on the following guideline.

i) The research results could contribute to overcome problems regarding basic human needs in Thailand.
ii) The research results could be applied to solve the specific problems in Thailand.
iii) The researches should not overlap with other researches conducted in other institutes in Thailand.
iv) The researches which have not yet been completed in international scientific society could not be done.
v) The researches should not cause environmental hazards such as pollutions and biohazards.

3.2.2 Analyses of the Contents of the Request

All the eight research subjects proposed by the Thai Government are judged to be appropriate for the purpose of the Project as above mentioned conditions. All the laboratories will cooperate and complement each other to the contents and methods of research. Each research has a close correlation in the process and their results. The followings are analyses of contents and methods of each research.

(1) Vitamin B deficiencies and carcinogens in hepatic tumour development

The highest three mortalities in Thailand are heart disease (24,290 cases in 1988), cancers (18,284 cases), and accidents and violence (16,491 cases). Hepatic cancer (1,672 cases in 1981 and 2,404 cases in 1983) ranked as the first cause of death in all cancers and then trachea, bronchus, and lung cancers (1,492 cases), stomach cancer (615 cases), and colon cancer (473 cases). According to statistics of geographic distribution of liver cancer in Thailand between 1980 and 1982, the frequency is the highest in the northeastern (10.7%) and north (21.6%) regions.

The average concentrations of nitrate and nitrite (carcinogenic initiator and precursor) in preserved and dried foodstuff such as fermented fishes and fish sauces are 24,354 ppm and 104 ppm, respectively, in northeast Thailand. N-nitroso compounds which are strong carcinogen such as dimethylnitrosourea (DMN) are also detected in these foodstuffs.

The other hand, riboflavin (vitamin B2) deficiency was detected 31% children aged 6-10 years in 1976 and 16% children aged 0-5 years in 1986 in northeast Thailand. 22% children aged 0-5 years had pyridoxine (vitamin B6) deficiency in this area in 1985. These statistical data has strongly suggested that high incident rate of hepatic neoplasm could associate with diet in northeast region of Thailand.

The CRI researchers have already finished their statistical surveys from provinces to villages. They have published these results as several scientific papers in well known international journals. Although they have collected the data suggested strong relation between vitamin B deficiency and liver cancers since 1980's, they have not yet started their scientific studies because of lack of experimental equipment.

Scientific correlation between vitamin B deficiency and hepatic cancer through laboratory experiments with model animals must be established to study the etiology of liver cancer. Morphological and

cytological changes should be examined. Acute and chronic effects of carcinogen may be studied. Enzyme activities and structural changes of nucleic acids could be also assayed biochemically.

Carcinogen such as DMN will be given to the vitamin B deficient and control groups of animals (rat). After appropriate term of feeding with special food, organs (liver, etc.) tissues, and cells should be resected from the animals and sometimes cultured. For this purpose, autoclave, laminar flow cabinet, and incubator should be used. Specimens and samples should be stored in ultralow temperature freezer.

Organs and tissues from experimental animals will be homogenized by homogenizer and homogenate should be fractionated to microsome, cytoplasmic, and nuclei fractions with regular and ultracentrifuge by routine cell fractionation method.

Several enzyme activities in microsome and cytoplasmic fractions should be assayed after purified through high performance liquid chromatography (HPLC).

DNA should be isolated from nuclei fraction by automated DNA extractor. Manual extraction method with phenol and chloroform could not be applied to this experiment because large number of DNA samples has to be extracted quickly from the fractions. Metabolite and derivatives of carcinogen and damaged DNA should be analyzed qualitatively by gas chromatography (GC) and quantitatively by gas chromatograph-mass spectrometer (GC-MS) and HPLC. Metabolites and derivatives of carcinogen which is labeled with radioisotope could be analyzed with liquid scintillation and gamma counters.

This may establish scientific correlation between nutrition habit and custom (vitamin B deficiency) and mechanism of carcinogenesis (hapatic cancer) through laboratory experiments with model animals. Results of this study should contribute not only for population in northeast region to improve nutritional status but also for Thai Ministry of Public Health to establish new strategy for public hygiene.

(2) Physiological and pathobiological studies on evaluation of industrial pollutants and pesticides

Thailand has rapidly industrialized in past decade. Raw plastic materials, that is, 4,500 metric tons of styrene, 5,000 tons of acrylonitrle, and 10,000 tons of methylmethacrylate in 1989. Imported gross of pesticides such as DDT, dieldrin, parathion has been 25,272 ton and around 2.5 billion bahts (ca. 14.5 billion yen) in 1988. Quantity of pesticides locally formulated was 35,626 tons in 1988. There is no original safety regulation and standard (maximum allow concentration; MAC, threshold limit value; TLV) in Thailand to protect not only nature (atmosphere, inland and ground water, and ocean) but also for people (work environment and labour hygiene). Each department and agency in Thai Government have followed American and European safety standards such as American Conference of Government Industrial Hygienists (ACGIH). However these standards should not be fully adopted to Thailand because life style, nutritional habit and custom, geographic condition, climate, and weather are differ from western countries. Case of accidental poisoning by petroleum products, drug poisoning, and poisoning by other poisons have been 23, 1,404, and 130 cases in 1989, respectively.

No researcher in Thailand has been carried out to determine the MAC and TLV values appropriate for local population. Although the CRI researchers have already started morphological assessment of toxic affects of pesticides with experimental animals and simple apparatus, they have been unable to begin further studies such as biochemical and pathobiological studies because of lack of equipment.

Acute and chronic effects of hazard materials such as industrial waste and pesticides in experimental animals (rats, etc.) should be studied through behavioral response, morphological, physiological, and biochemical studies. Different amount or concentration of toxic compounds should be fed to experimental animals. Behavioral response should be studied by cooperation with pharmacology laboratory in CRI because generally these hazard compounds attack to nerve system. Morphological, physiological, and cytological researches would be shared by microscope with immunology laboratory. Biochemical studies should be conducted in this laboratory.

Nervous system, heart, liver, kidney, and blood samples should be resected from the animals. Operation may be done in laminar flow cabinet, and apparatus, culture medium, and buffers should be sterilized by autoclave. Tissues, organs, and cells should be disrupted by homogenizer

and homogenate and blood should be fractionated by routine cell fractionation method. Effects of hazard compounds against nerve system should be analyzed by HPLC, GC, and GC-MS after extraction of their metabolites. Enzyme activities such as plasma acetylcholine esterase may be assayed with HPLC and GC after extraction. Effects of toxic materials on DNA should be examined by HPLC after extraction from nuclei fraction by automated DNA extractor. Liquid scintillation and gamma counters should be applied when hazard materials labelled with radioisotope should be used in experiment.

Results of this study would contribute to provide fundamental data and recommendation not only to determine safety regulation and standard (MAC and TLV) for protection of people and environment but also to help Thai government regulatory agencies make legislation for environment and health protection.

(3) Biodegradation of toxic industrial chemicals and pesticides

Toxic compounds such as industrial wastes and pesticides should cause pollution if these would not been treated appropriately. This research is deeply correlated to former research that is study to determine safety regulation and standard (MAC, TLV) for environmental protection in Thailand to prevent pollution. Although researchers in developed countries are attempting to synthesize plastics which can be degraded by microorganisms, the purpose of this research is to creat new microorganisms for biodegradation of toxic materials such as industrial waste and pesticides by genetic engineering methods.

Soil samples will be collected from the nationwide. Microorganisms, that is fungi and bacteria should be isolated and cultured to obtain pure strains. Several soil samples from many parts of the nation to isolate microorganisms have been already collected by routine microbiological techniques. Ability of biodegradation of toxic compounds could be assayed by screening method. Several kinds of incubators and centrifuges and ultralow temperature freezer may be used for culture, isolation, assay, identification, and storage of microorganisms.

Once pure strains of microorganisms which can degrade hazard compounds have established, mutant which has the stronger ability of biodegradation will be developed with combination of old fashion methods with chemical mutagens and UV and gamma rays and modern biotechnological methods. There is no place in Thailand where has been set up state-of-the art equipment for genetic engineering.

Genetic materials and enzymes which involve in degradation of toxic compounds could be isolated and identified. The genes should be isolated with gel electrophoresis and multiplied with polymerase chain reaction (PCR) machine. Character of DNAs involved in biodegradation should be determined with automated DNA sequencers. These genes that may be as episome should be transduced and/or integrated into microorganisms with restriction enzymes and polymerases to obtain new organism which has the higher biodegradation activity. Enzymes related to degradation reaction could be isolated with gel electrophoresis. Primary structure of enzymes should be determined with automated peptide sequencer.

The results from this research should contribute to solve environmental agenda not only in Thailand but also other developing countries in southeast Asia.

(4) Development of disease resistant rice

Rice is main foodstuff for Thai people and one of major export product (the third place in 1988). Area of rice field in Thailand is 11.8 million ha. Damaged areas of rice field in 1981 is 2,640,372 ha (22.3%) by insects, 566,100 ha (5%) by diseases, and 1,252,054 ha (10.6%) by small animals such as rats. It is possible to enhance yield of rice if these damages could be reduced. Focus of this research is to develop disease resistant rice by biotechnology.

Different specimens may be collected from the nationwide and cultured to obtain disease resistant strains by screening method. A couple of specimens of rice have been already collected from the several areas of the nation. Screening plants may be cultured to obtain pure strain and multiplied. For this purpose, autoclave, laminar flow cabinet, and illuminated plant growth chamber should be used. Genetic materials involved in disease resistance may be extracted from pure strain by gradient centrifugation with ultracentrifuge and purified with automated preparative electrophoresis.

Character of the isolated DNAs or mRNAs may be analyzed high performance electrophoresis (HPE) and automated DNA sequencer. DNAs or RNAs could be synthesized by polymerase chain reaction (PCR) machine with restriction enzymes and polymerase. Cistron (genotype) related to disease resistance (phenotype) may be composed of multiple genes. It is almost impossible to sythesize manually such long and large number of genes without PCR machine. Synthesized disease resist genes should be integrated into rice to creat new species by genetic engineering method.

The other hand character of disease resistance may be located in microorganism(s) which live in or on host. In this case the microorganism should be isolated from rice and cultured to obtain pure strain with incubator shaker. After identification by screening method bacterial genes or episome related to disease resistance could be isolated with gradient centrifugation and gel electrophoresis. Characterization, multiplication, and integration of bacterial genes should be done by the same methods as mentioned above.

After development o disease resistant rice(s), the speices should be multiplied at the Ministry of Agriculture and Cooperatives to distribute and farmers. Rice production could be enhanced by created species. Development of new species should contribute to improve not only quality of life of farmer in rural area but also Thai economy through increase of rice export. Although other institution in Thailand also try to develop new species of disease resistant rice by routine screening method, it is expected to take a long time.

(5) Synthesis of oligosaccharides by enzyme reactions

Production of cassava and cane in 1988 has been 22.7 million tons and 27.2 million tons in Thailand, respectively. In the same year export of cassava ranked the sixth and sugar was the nineth places in value. It is clear that these are important export products for Thailand if it would be considered rice production (18.9 million tons) and its export amount (the third place in value) in 1988. Three crops which have produced more amounts than rice have not been utilized effectively in Thailand. This research proposes to study the enzymatic synthesis of oligosaccharides that can be contributed to improve quality of life for Thai people through several application.

Tooth decay is a major concern and is due to production of acidic compounds by bacteria that adhere to teeth with polysaccharides. Dental plaque formation might be inhibited by suitable oligosaccharides antagonists such as isomaltulose. Oligosaccharides obtained by enzymatic synthesis should be examined their ability to inhibit dental plaque formation.

Several tumour antigens are oligosaccharides. Lectins are glycoprotein and some of them can bind to surface of tumour cells. It is possible that patterns of oligosaccharide at lectin binding site on the surface of cell may be applied to characterize different type of cancers for diagnosis and therapy.

The other application of synthesized oligosaccharides is for food additives, medicines, and transfusion fluids. Almost all of important oligosaccharides for these purpose have been imported from foreign countries. If Thailand can synthesize by herself trade imbalance should be improved.

Polysaccharides, starch, and sucrose may be extracted from cassava, corn, and cane and hydrolyzed chemically or enzymatically to glucose or other monosaccharides. Glucose should be converted to other monosaccharides such as fructose and galactose with racemases. Routine methods in enzymology with centrifugation, ultrafiltration, column chromatography, and affinity chromatography could be used for isolation and purification of racemases.

Isolated glycosidases from microorganisms and plant tissues can be used for oligosaccharide syntheses in specific condition by reverse reaction, though these enzymes originally catalyze degradation reaction from polysaccharides and oligosaccharides to monosaccharides. Although isolation and purification of a couple of glycosidases from several plants and bacteria have already started with experiments of old fashion style, yield of these enzymes has been very low. Modern sophisticated equipment and techniques are essential to get highly purified enzymes in good yield for specific reactions.

The enzymes should be purified and characterized by affinity column chromatography, gel electrophoresis, and HPLC. Enzyme activity, substrate specificity, and reaction mechanism should be studied spectrophotometrically and effective condition to synthesize oligosaccharides by reverse reaction could be determined. Synthesized saccharides should be isolated, analyzed, and identified by HPLC.

It is highly evaluated that intention of the research is not usage of these crops as foodstuffs by improvement of species but syntheses of oligosaccharides for raw materials of food additives, diagnostic and therapeutic medicines, and transfusion fluids from monosaccharide produced from the crops. Success of this research should induce not only effective usage of resources but development of new industry to produce export goods in Thailand.

(6) Development of immunodiagnostic methods for tropical infectious diseases

Some infections diseases are unique to Thailand such as meliadosis which is a bacterial infection caused by Pseudomonas pseudomallii and

gnathostomiasis which is a parastic infection caused by Gnathostonma spinigerum. Cholangiocarcinoma induced from chromicaly infection of a liver fluke (Opithorchis viverrini) is a malignant disease of the biliary system. Major concern in diseases are meliodosis and cholangiocarcinoma in northeastern region and gnathostomiasis in central area of Thailand, respectively. Meliadosis infection causes high fever, jaundice, breath difficulty, and leukocyte destruction and its mortality is very high as 32%. Liver fluke and parasite have infected from insufficiently cooked foodstuffs such as fresh water fishes, frogs, and snakes. Dog and cat play as intermediate host. Parasite larva lives under skin after infection and forms lump and abscess. Occasionally larva enters eye, lung, abdomen, and brain. Case of these infective and parasitic diseases have been 98,227 in 1987 and cases of conjunctivitis has been 223,593 in 1988.

No definitive diagnosis for these diseases has been available. Current test method is not only time consuming but also lack of specificity and poor sensitivity, so that patients may die before they are diagnosed and properly treated. It could be possible to save many lives if antigens in patient blood against these tropical diseases could be effectively detected.

It seems that immune responses caused by Pseudomonas, liver fluke, and parasite infections are too slow to detect even if antibodies in host are formed by organisms themselves, their metabolites, or secretory materials. Although tumour markers (specific molecules produced and/or secreted from cancer cell) for melanoma, rectal carcinoma, pancreatic caricinoma, neuroglianoma, and thymoleukemia have been already found, it is difficult to find tumour marker for cholangiocarcinoma which is induced from liver fluke infection in many cases in Thailand.

Purpose of this research is to establish new diagnostic method with monoclonal antibody which can be detected disease infections quickly, specifically, sensitively, and inexpensively.

The CRI researchers have finished their statistics analysis of collected data of several tropical diseases from nation wide and the results have already reported to domestic and international scientific journals. They also have started preliminary experiments to diagnose one of these diseases by routine immunological method, however they have found that mass production of monoclonal antibody against the diseases have been essential to develop effective immunodiagnostic method with modern equipment.

Combination of several specific techniques and methods is essential to produce monoclonal antibody. Monoclonal antibody is produced from the

hybrid cell that is prepared by cell fusion between B lymphocyte and tumour cell such as myeloma cell. The fusion cell has both potential to form antibody (IgG) from B lymphocyte and to multiply rapidly from myeloma cell so that the cell can produce pure and large amount of monoclonal antibody in a short time.

B lymphocytes with fluorescence marker which could produce specific antibody should be isolated from patient blood specimen through cell sorter and cultured for multiplication in CO2 incubator. The cultured cells should be collected by centrifugation and the cells should be fused with myeloma cells under focusing of fluorescence microscope equipped with micromanipulator. Fusion cells should be characterized on microplate and isolated by cell harvester and/or cell sorter. Antigen-antibody reaction may be assayed on microplate and confirmed by fluorescence microscope. Monoclonal antibody should be purified through affinity column chromatography.

Once the new immunodiagnostic methods to detect these diseases in early stage have been established, the methods should be transferred to hospitals and regional clinics through Mahidol University Applied and Technological Service Center. Results from this research should contribute to save human life and to improve people's life not only in central and northeast Thailand but also in other tropical countries.

(7) Pathophysiological studies on hypoxemia by thalassemia

Thalassemia is one of dominant inheritance disease and is caused by imbalance synthesis of beta chain of haemoglobin E in erythrocyte. According to WHO, around 100 thousand new patients should be found in the world each year. In Thailand, 30 to 40% of whole population (51.8 million) should carry thalassemia gene. Conspicuous rate by marriage between the gene carriers is estimated around 5% (ca. 906.5 thousand people) in Thailand and this number of patient expectancy is very large.

Erythrocyte is destroyed itself before maturation in blood vessel and hypoxemia with debility and pain in extremities is occurred. Patient has aggregation of blood cells in blood vessel, nosebleeding, infection by impairment of immune system, hepatic hypertrophy, and gallstone. Iron which is released from haemoglobin after destruction heavily deposits and overloads everywhere in the body. Almost all of patients may die before 15 years. There is no fundamental method not only for therapy but also for symptomatic treatment. Operation of spleen resection (splenectomy), blood transfusion, and oxygen mask are only ways to reduce pain from

patient temporarily.

Purpose of this project is to find therapeutic method to release pain and to prolong life span of patient. Relation between progress and mechanisms of disease has not yet been cleared so that symptoms and biochemical mechanism must be studied.

There are several difficulties just to survey and to take statistic data. First of all many patients can't go to doctor because of poverty. Secondary family of patient doesn't want to report the thalassemia to the doctor or government officer because this is one of dominant inheritance disease. Thirdly almost all of patients have gone before fifteen years old. In Thailand only small number of patients in established people have been able to be hospitalized. Limited cases and progresses of this disease have been reported.

It is essential to study this tragic disease in cell level to develop more effective therapeutic method. Mechanism of blood cell aggregation in blood vessel may be studied by impedance aggregometer. Blood sample of patient should be analyzed with computerized cell counter. Blood cells could be fractionated through cell sorter and by centrifugation.

Iron deposit may relate to calcium metabolism so that distribution of calcium ion in erythrocyte should be analyzed by intercellular calcium analyzer. Iron which may be toxic peroxide and/or radical state by redox reaction should be analyzed by electron spin resonance spectrometer (ESR). Enzymes involved in this reaction should be assayed with luminescence analyzer. Peroxide compounds may be analyzed and identified through HPLC. Short half life radioisotope such as I125 will be given to patient and labeled enzymes and membrane proteins isolated from blood cell may analyzed with liquid scintillation and gamma counters.

It is no doubt that the study is important in Thailand because of number of patient. The results of this research should contribute to find therapeutic method to release pain and to prolong life span of patient.

(8) Studies on cerebral malaria

Malaria is still major public health concern in many tropical and developing countries included Thailand. Cases of Malaria in Thailand have been 130,304 (559 deaths) in 1987, 131,390 (490) in 1988, and 100,528 (276) in 1989, respectively. Drug resistant malaria against chloroquine, pyrimethamine, and sulfadoxine has distributed in Colombia and north part of Brazil in South America, Myanmar, Thailand, Malaysia, and Indonesia in southeast Asia, and Kenya, Tanzania, Nigeria in central Africa. This drug

resistant malaria has been major cause of cerebral malaria because larva (merozoit) attacks to brain. 60% of malaria patient in Thailand has been caused by drug resistant malaria (Plasmodium falciparum) and 7% case out of 60% has been cerebral malaria. Mortality of cerebral malaria has been very high as around 40%.

To develop and/or find new medicine for chemotherapy of cerebral malaria is urgent matter. There are several reasons why effective medicine against malaria has not yet been developed. One is that host has never obtain immunity. The reason is that merozoit of malaria lives in host cell (erythrocyte) such as bacteria of Mycobactrium tuberculosis and Salmonella typhi, fungi of Candida and Hystoplasma, and merozoit of Toxoplasma and Tripanosoma instead of intertissues or interorgans. Antibody produces through blood and lymph system, so merozoit in red cells is protected from B cell (leukocyte) by cell membrane of erythrocyte. Other is that merozoit can easily obtain drug resistance. We have still no idea of mechanism how merozoit acquires this resistance.

Screening of new therapeutic medicine against cerebral malaria which is caused by drug resistant malaria is urgent matter. Antimalarial activity of newly found compounds may be examined in this laboratory.

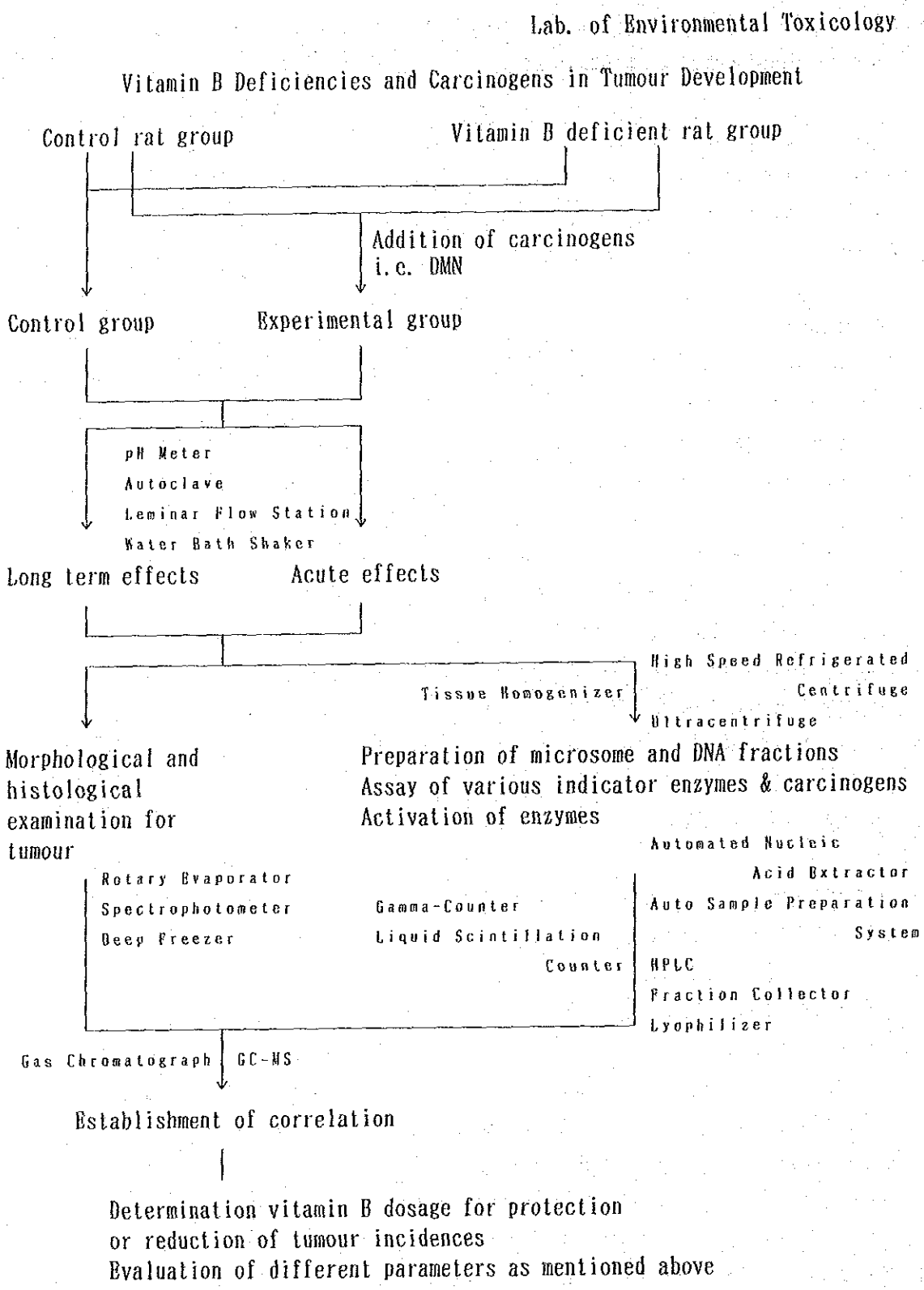
The researcher in chemistry laboratories of CRI have already started to extract effective compounds from plants. They also have modified these compounds to obtain more substantial medicines. The other hand new drugs for chemotherapy have been tried to synthesize chemically. These attempts have not yet completed. The researcher in this laboratory have waited progress in the chemistry laboratories.

New medicine will be given to experimental animals (rats, etc.) infected malaria. Pathophysiological and immunological studies will be shared with pathobiology and immunology laboratories in CRI, respectively. Behavioral and physiological changes for toxicological studies should be observed. Behavioral changes of experimental animals should be examined with tail flick apparatus and treadmill because drug resistant malaria attacks central nerve system. Physiological changes of model animals should be examined by respiratory analyzer and polygraph. Pharmacological and Morphological changes of experimental animals in central nerve system, cardiovascular system, and respiratory system could be estimated with organ bath after resection. Biochemical examinations such as toxicity and pharmacological effect of new drugs should be studied through assay of enzyme activity after isolation by routine cell fractionation method and purification by column chromatography.

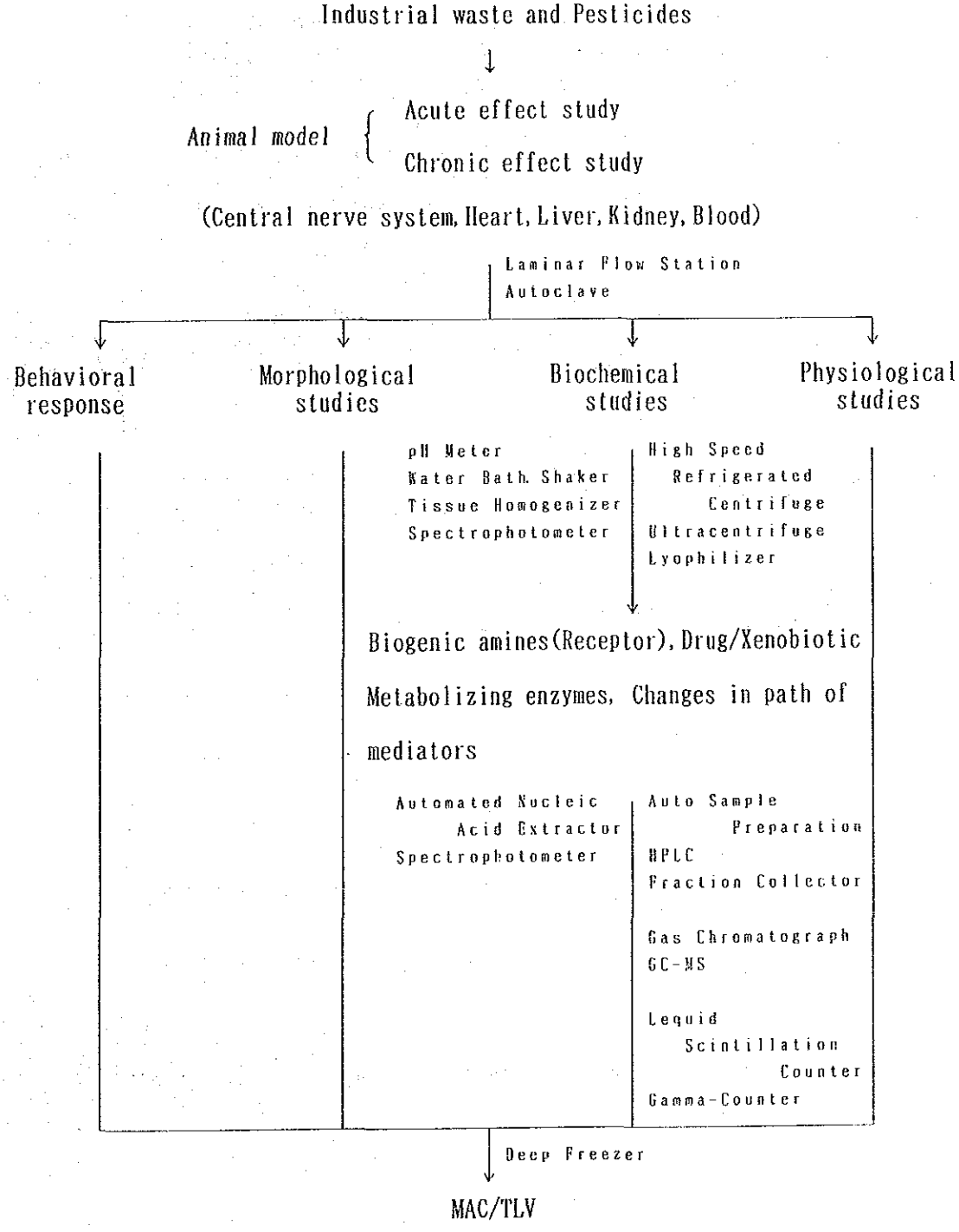
When effective medicine for malaria has been found, the drug should

be applied to human therapy through the Ministry of Public Health. The results from screening of new therapeutic medicine against cerebral malaria could contribute to save human life and to reduce number of patient of drug resistant malaria.

3.2.3 Flow Chart of Researches

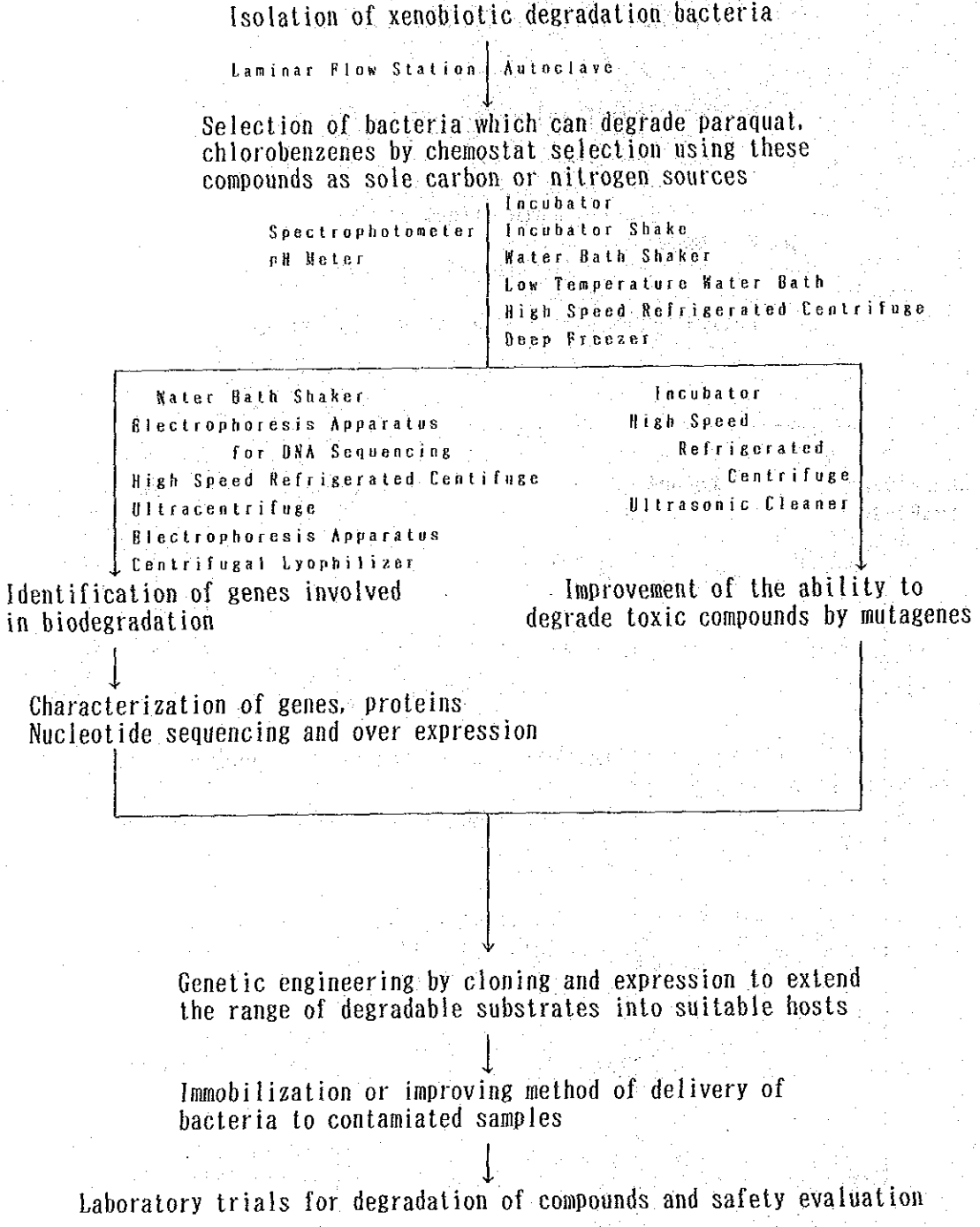


Physiological and Pathobiological Studies of Evaluation of Industrial Pollutants and Pesticides

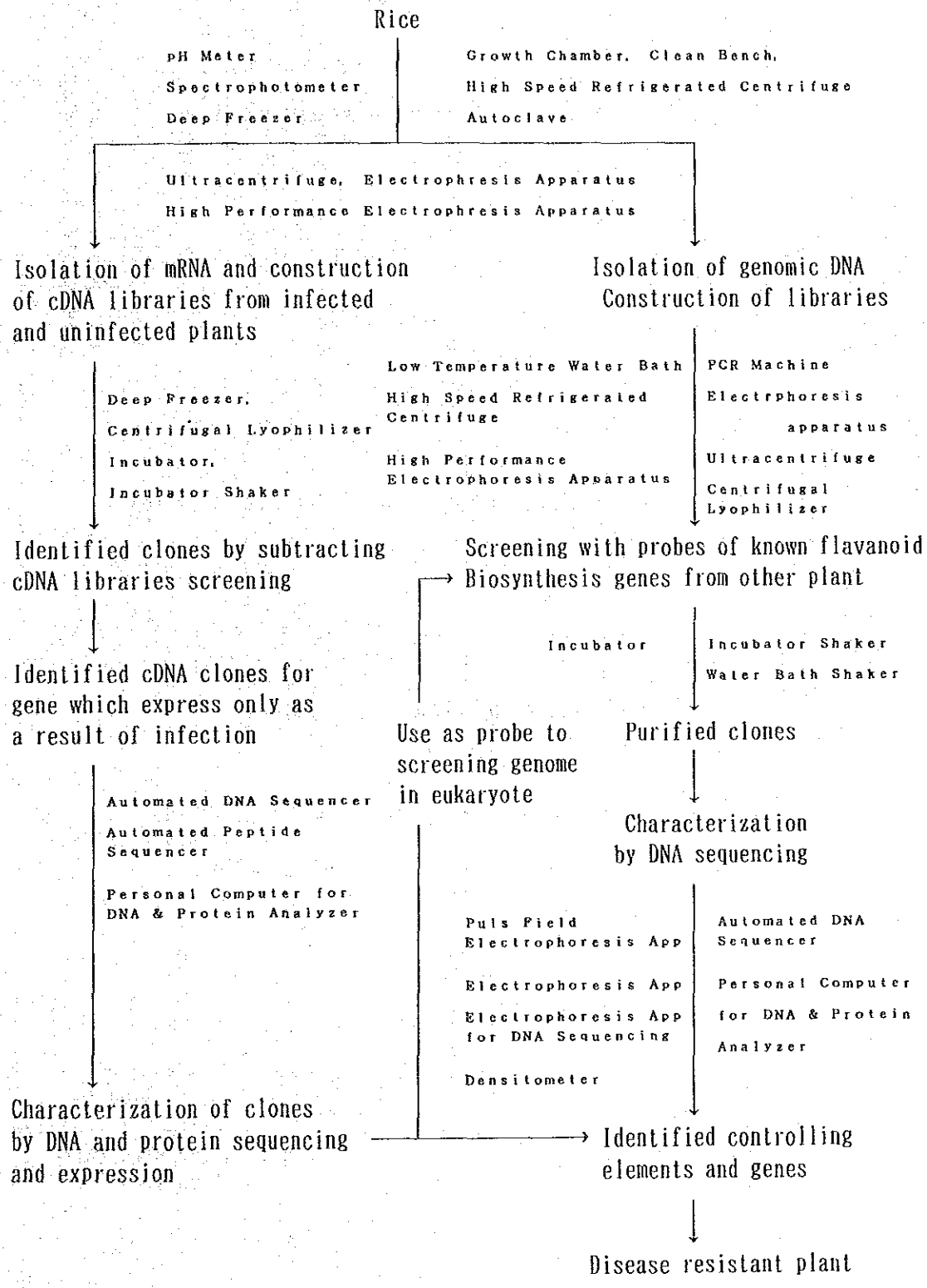


MAC : Maximum Allow Concentration
TLV : Threshold Limit Value

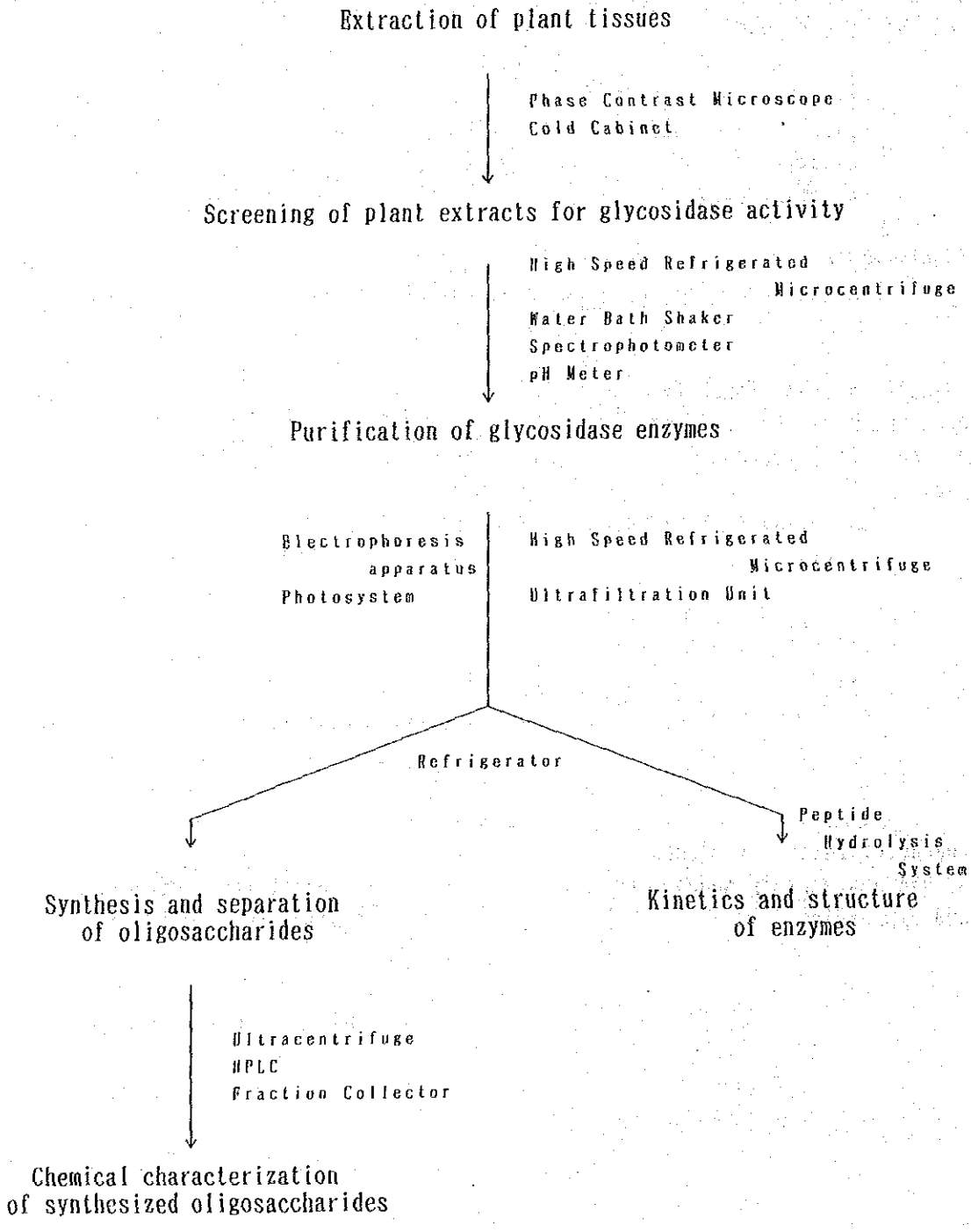
Biodegradation of Toxic Industrial Chemicals and Pesticides



Development of Disease Resistant Rice



Synthesis of Oligosaccharides by Enzyme Reactions.



Development of Immunodiagnostic Methods for Some Unique Tropical Infectious Diseases and Some of Their Complications

Diagnosis of infectious disease (Melioidosis, gnathostomiasis)

Phase Contrast Microscope | Clean Bench

Obtaining speciments

pH Meter | Autoclave
Electrophoresis Apparatus

Identification and characterization of antigens

pH Meter
Water Bath Shaker
Automated Microplate Reader
Electrophoresis Apparatus

Isolation of appropriate antigens

Water Bath Shaker

Construction of DNA probe

Automated Protein Synthesizer | Lyophilizer
Deep Freezer

Detection of organiam directly from clinical specimens

High Speed Refrigerated Microcentrifuge

Monoclonal antibody production

Fluoroscence Microscope
Automated Microplate Reader
Cell Harvester
Fraction Collector
High Speed Refrigerated Microcentrifuge
Freezer

Detection of antigen directly from clinical specimens

High Speed Refrigerated Centrifuge

Preparation of specific antigen for detection of antibody in clinical specimens

Fluoroscence Microscope
High Speed Refrigerated Centrifuge
Automated Microplate Reader
Cell Harvester
High Speed Refrigerated Microcentrifuge

Tumour marker for cholangipcarcinoma (Complication of liver fluke infection)

Dissecting Microscope | Clean Bench

Specimens

Low Speed Refrigerated Centrifuge

High Speed Refrigerated Centrifuge | Fraction Collector | Refrigerator | Fluoroscence Automated Cell-Sorter & Analyzer

Induction of Tumour in experimental animals

CO_2 Incubator
pH Meter

Tumour mass from patients

CO_2 Incubator
pH Meter
Electrophoresis Apparatus
Freezer

Obtaining tumour cell line

Incubator
Water Bath
Shaker

Incubator Shaker

Physicochemical & immunological characterization

Water Bath Shaker
Electrophoresis Apparatus

Identification of appropriate tumour components

Electrophoresis Apparatus

Determination of specificity and evaluation of their potential

Automated Microplate Reader
Electrophoresis Apparatus

Production of monoclonal antibody

Fluoroscent Microscope | High Speed Refrigerated Microcentrifuge
Cell Harvester | Electrophoresis Apparatus
Fraction Collector | Freezer

Development of method for early detection on serum bile, etc

Fluoroscence Microscope, Spectrophotometer
Automated Microplate Reader, Cell Harvester

Pathophysiology of Hypoxemia in Thalassemia

Genetic defects and the imbalance synthesis of human globrin chains

↓ Dissecting Microscope, Low Temperature Water Bath, Autoclave, pH Meter

Premature destruction of the red blood cells

↓

Hypoxemia

Platelets, white blood cells, vascular endothelium
- -are primarily affected
- -may be aggregated
- -block the micro-circulation

↓ Auto Cell Counter, Impedance Aggregometer, Calcium Analyzer, High Speed Refrigerated Centrifuge, Ultrasonic Cleaner, High Speed Refrigerated Microcent-rifuge

Heavily iron overloaded and deposited in body tissues & organs — Heart, kidny, Liver, Lung

↓ Electron Spin Resonance Spectrometer

Generation of highly active oxygen "Free radicals" — Lipid peroxidation

↓ HPLC, Luminescence Analyzer, Spectrophotometer, Liquid Cintillation Counter, Deep Freezer

Damaged cell membranes — Depletions of natural antioxidants (Vitamin C & E); Release of pathologic "mediators" from the affected cells

Cerebral Malaria