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ASSISTANCE IN THE PRODUCTION OF PHARMACEUTICALS FROM THE THAI TRADITIONAL PHARMACOPOEIA

DP/THA/87/010

THAILAND

Technical report: Evaluation and recommendations*

Prepared for the Government of Thailand
by the United Nations Industrial Development Organization
acting as executing agency for the United Nations Development Programme

Based on the work of Mr. Pitambar Somani, M.D., Ph.D.
Cardiovascular expert

Backstopping Officer: Dr. R.O.B. Wijesekera, Chemical Industries Branch

United Nations Industrial Development Organization
Vienna

* This document has not been edited.

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INTERIM REPORT

Prepared by: Pitambar SOMANI,M.D.,Ph.D
Cardiovascular Expert

UNDP Project DP/THA/87/011/01

Modern Pharmaceutical Formulations based on the Thai Traditional Pharmacopoeia

The Thailand Institute of Scientific and Technological Research (TISTR)

November 4, 1988 to December 31, 1988

BACKGROUND

The major objectives of the program DP/THA/87/011/01 are to provide assistance in the pharmacological and toxicological screening and testing of various drugs derived from the traditional Thai pharmacopoeia, with the primary emphasis being in the field of cardiovascular drugs. The project was started in 1984, and since that time many significant achievements have been accomplished, including the industrial production of Garlic Natura, and initial identification of several possible natural substances with potentially significant usefulness in the treatment of various cardiovascular diseases. Many of these plant materials were identified based upon the long tradition of their successful use by the local practioner of Thai medicine in patients with these disorders. Since development of drugs may take many years, possibly between 7-15 years from the initial stage of identification and early screening for the claimed pharmacological activity, followed by a complete pharmacological and toxicological profile leading to clinical testing, multi-disciplinary team of experts is an essential requirement for obtaining the final approval of the Food and Drug Administration for these drugs in order to be able to market them for general use. During the early stages of the project it was identified that while the infra structure was established in the Pharmaceutical and Natural Products Division (PNPD) at TISTR, through considerable input from the Government and good leadership, there was a need to surmount the special requirements of the pharmaceutical industry of detailed pharmacological and toxicological workup with a candidate drug before adequate clinical trials can be organized and completed. Thus, external expertise to help the staff of PNPD in setting up detailed experimental protocols for screening and further evaluation of the plant extracts from the traditional sources was felt to be necessary, and Dr. Somani was appointed as the UNIDO Technical Expert in Cardiovascular Pharmacology, with his extensive experience in basic and clinical development of various classes of drugs for human use.

OBJECTIVES

Based upon the recommendations in the project reports and initial discussions with Mrs. Sasithorn Wasuwat, Director, PNPD, after my arrival in Bangkok on November 4,1988, the following objectives were agreed upon:

A. SCREENING OF THE THAI MEDICINAL PLANTS FOR CARDIOVASCULAR ACTIVITIES.

The screening of the drugs from plants already identified to possess potential activities on the cardiovascular system should progress for the following activities:

1. Antihypertensive,
2. Cardiotonic, or cardiodepressant,
3. Antianginal or coronary vasodilator.
4. Antiarrhythmic, and
5. Others, e.g. cholesterol lowering.

The following plants have already been identified, and their extracts have already been prepared to begin immediate laboratory experiments, once the methods have been set up in PNPD:

1. Zingiber cassumunar (rhizome)
2. Nelumbo nucifera (lotus embryo)
3. Tinospora crispa L.(Borapet)
4. Cyperus rotundus Linn (Ya-Haw-Moo)
5. Salix tetrasperma (Sanun)
6. Allium sativum (garlic natura)
7. Other plants to be identified and added to this list.

B. STEPS NECESSARY TO DEVELOP A DRUG FROM INITIAL SCREENING TO THE FDA APPROVAL.

Since a new drug development requires extensive pharmaco-logical and toxicological testing, followed by clinical trials, a well planned approach is necessary to bring these drugs into market. Adequate plans should be drawn for each group of drugs, including the relative position with respect to currently available drugs, as well as the use of adequate control experiments in their pharmacological testing, and clinical pharmacological evaluation. Dr. Somani will provide an important input in this process with his extensive background in basic and clinical pharmacology by holding review sessions with the staff members of PNPD, and then formulating the details of the IND (Investigational New Drug) and NDA (New Drug Application) approaches. Although the Thai traditional drugs have been used extensively for many years, if not many centuries, their active constituents still must receive the same degree of extensive preclinical pharmacological and toxicological workup as any new synthetic drug from modern medicine.

REPORT

I. CARDIOVASCULAR SCREENING

After a careful review and evaluation of the equipment, facilities and the technical staff available at PNPD, and within the time frame of my stay at TISTR for the period of two months, it was decided that I should review the known cardiovascular activities of the plant material of interest to this project, and then to formulate a plan of action to provide maximum benefit to this project. A survey of the cardiovascular activity of medicinal plants according to Thai Traditional Pharmacopoeia was made and the following information was compiled:

NAME	PART	TRADITIONAL USE	SCIENTIFIC INFORMATION
Aegle marmelos	root	stuffy feeling in the chest	
Allium sativum (Garlic)	bulb	atherosclerosis antihypertensive	cholesterol lowering, antithrombotic (methylallyltri-sulfide), fibrinolytic, antihypertensive(many references)
Amomum xanthoides	seed	antihypotensive	hypotensive(fruit) (i.v. injection of 50% alcohol extract in dogs) J. Med Assoc Thailand 54: 490, 1971
Centella asiatica	whole plant	heart tonic	hypotensive(iv 50% alcohol extract) J.Res.Indian Med 4:160,1970; J.Med Assoc.Thai 54: 490, 1971.
Cyperus rotundus	bulb	heart tonic ischemic heart	hypotensive (50%alcohol extract) J.Med Assoc.Thailand 54: 490, 1971

NAME	SOURCE	TRADITIONAL USE	SCIENTIFIC INFORMATION
Measua ferrea	flower	heart tonic	
Mimusops elengi	flower	relieve stroke, blood tonic	
Nelumbo nucifera (liensinine) (neferine) (methylcory - palline etc)	embryo	coronary vasodilator	antihypertensive (J. Nat Prod. 49: 47, (1986)
Ochrocarpus siamensis	flower	heart tonic	
Pandanus odoratus	leaf	heart tonic	
Salix tetrasp- erma	stem, leaf.	heart tonic	increased force and rate of per- fused frog heart (TISTR Res Proj 17/11 (1969).
Uncaria spp.		antihypertensive	(Zhongguo Yaoli Xuebao 4: 114, 1983)
Zingiber cassumunar	rhizome		negative inotropic and chronotropic (isolated rat (atria) TISTR expt. work.
Zingiber officinale	rhizome		Stimulation of resp & vasomotor center. hypotensive (I.V.) in rats; J. Phar Sci. 41: 1174, 1982 cholesterol lowering

It should be emphasized that this summary is based upon the information available from the usual sources, and it would be very important to perform a careful and exhaustive review of the published and patent literature to establish exactly what has already been done thus far with respect to the cardiovascular actions of these drugs. In this respect, recent agreement of collaboration with Central Drug Research Institute (CDRI), Lucknow, India would prove most invaluable, since they have already screened many plant materials based upon the Indian traditional medicine

To help establish experimental protocols for screening cardiovascular activities of the Thai medicinal plants, it was decided to demonstrate the activity of several most promising drugs at first, and then to utilize these methodologies to continue further work with the remaining plants during the next 12 months. As my technical mission has been split into two parts, I shall outline the work that was accomplished while I was in Bangkok during this visit, and then propose additional work for the next 12 months which will continue to be carried out at PNPD and will be reviewed upon my return visit next year.

II. SCREENING FOR ANTIHYPERTENSIVE ACTIVITY.

Experimental Preparation. Male adult Wistar rats weighing 275-300 gm were anesthetized with 40 mg/kg i.p. pentobarbital sodium, supplemented with urethane (.875 mg/kg i.p.). Additional urethane was given as necessary. The femoral vein was cannulated with a fine polyethylene tube for injection of drugs. The carotid artery was cannulated for recording of the systolic and diastolic blood pressure via a strain gauge transducer. Heart rate was counted from the blood pressure tracings. The arterial cannula was filled with heparin (50 units/ml) saline solution.

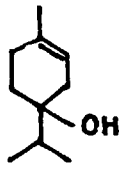
Protocol In each experiment, the drug was prepared in an appropriate solvent, and the effect of 3-4 doses of each drug was investigated in each animal. The response with a standard drug, i.e.,epinephrine (adrenaline, 7 ug/kg) was first obtained to establish that the animal was showing normal responsiveness to the drugs.The effect of the solvent was also tested, followed by the administration of the experimental preparation. No drug was given at less than 10 min interval between each dose.

Observations. The following six drugs were tested in at least 2 animals each, and the results with each Thai plant extract are summarized as follows:

1. Ginger Oleoresin. This extract from the rhizome of the plant Zingiber officinale contains several active principles, including gingerol with 4, 6 or 8 (CH_2) groups in the molecule. Ginger oleoresin was tested in the doses of 0.1, 0.2, 0.4, 0.8 and 1.6 mg/kg intravenously. The drug produced a moderate increase in both systolic and diastolic blood pressure in a dose dependent manner. The maximum increase in blood pressure was 20-30 mm/Hg, and the duration of action was from 5 to 10 min. There were no changes in heart rate in the doses tested.

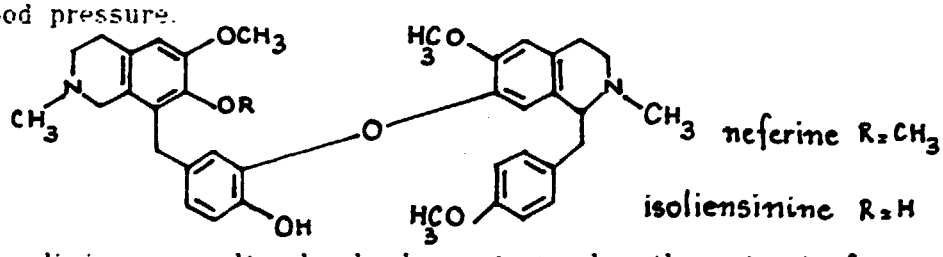
Further experiments need to be performed to study the mechanism of its vasopressor action, duration of action, and whether or not this drug has a similar activity when it is given orally. The activity of individual chemical components also need to be evaluated. However, although these preliminary results show biological activity with ginger oleoresin on the cardiovascular system, with the limited time and resources available at present, further work with this drug should be at a lower priority, since the clinical usefulness of this vasopressor action is not as obvious as for the other groups of drugs already tested at PNPD.

2. Terpinen-4-ol. This drug, a highly purified chemical whose structure is well known (see figure below), is derived from Zingiber cassumunar rhizome, and has been reported to produce negative inotropic and negative chronotropic actions in the isolated rat atria When given to the anesthetized rats. inthe present screen, the drug produced a dose dependent decrease in both systolic and diastolic blood pressure.



Although the hypotensive action of this highly purified drug confirmed its cardiovascular activity, I recommend that a thorough search of the literature be carried out to determine whether the antihypertensive activity of this chemical class of drugs has already been tested and reported, since its structure is fairly simple and well known, before further studies are performed.

3. Nelumbo nucifera (Lotus). The extract obtained from the embryo of the lotus seed, which has been identified to contain several active principles, including neferine and isoliensinine (see figure below), was injected intravenously in the dose range of 3.2 to 12.8 mg/kg, and was found to produce a dose-dependent decrease in both systolic and diastolic blood pressure.



These preliminary results clearly demonstrate that the extract of this Thai plant has potential antihypertensive activity, and definitive experiments need to be planned and carried out to extend these observations, including the mechanism of action, oral activity, role of its active ingredients etc.

4. Cyperus rotundus. Eating the bulb of this plant is believed to keep a person very healthy and looking very young despite increasing age. The extract of the bulb of Cyperus rotundus was injected intravenously in two rats, and although a slight increase in both systolic and diastolic blood pressure was observed, there was no dose response relationship. It may be possible that further experiments in the models for hypertension or in the model to study its effects on myocardial hypoxia may show some cardiovascular activity, but at present its effect on blood pressure appear to be minimum.

5. Tinospora crispa L. This is a newly identified drug in Thai traditional medicine, and at present no special clinical use has been ascribed to this drug. The extract of this plant was tested in the rat model, and a very gradual but striking decrease in both systolic and diastolic blood pressure was observed. Further experiments were carried out in two control and two drug-treated rats where a single dose of the extract was injected to determine the extent and duration of the

antihypertensive action. It was found that unlike the effect of the solvent in control experiments, the extract of Tinospora produced a slow decrease in blood pressure which was maximum in 10-20 mm Hg with 20-30 min duration.

These observations suggest that further work would be very useful with this plant, including the identification of the active principle.

6. Garlic natura. This water soluble extract of garlic bulb is quite different from the traditional garlic oil, since many of the essential oils are removed in the spray-drying process of its preparation. Intravenous injection of this preparation did not result in any acute change in blood pressure, but a careful analysis of the records suggested that with each dose, both systolic and diastolic blood pressure were slightly lower at about 5 min after the injection as compared to the pre-drug pressures. Further experiments were then carried out in two additional rats where only a single large dose (12.8 mg/kg) of Garlic natura was injected. As compared to the solvent controls, it appeared that Garlic natura was able to induce a slow and gradual decline in both systolic and diastolic blood pressure which was maximum between 20-30 min.

Further work is recommended with Garlic natura as well as with its odorless spray dried preparation, along with a comparison with the standard garlic oil preparation on the cardiovascular system.

III. SCREENING FOR CARDIOTONIC ACTIVITY

Experimental preparation. Guinea pig atrial preparation. The standard technique for the isolated guinea pig atrial preparation was utilized in the present study. After removing the heart quickly after stunning the guinea pig, the atria were removed and placed in an oxygenated buffer solution (Kreb-Hensleit) at 36 C. The atria were attached to the force displacement transducer with a fine silk thread to record the rate or force of contraction.

Protocol. Right atria. The right atria has the sinus pacemaker activity which allows it to beat spontaneously at a rate of between 150 and 180/min. Thus, the effect of a drug under study on heart rate can be investigated in this preparation. In order to compare the effect of an unknown drug from the plant source, it also is important to show that the preparation has a normal response to a standard drug. In each experiment, after the atrium has been allowed to stabilize, response to isoproterenol ($5X10^{-8}$) is first obtained, the peak changes normally occurring in 1-2 min. After several washes, the test drug is added to the tissue bath at 5 min intervals, and the effects of increasing drug concentrations are tested in the same preparation to obtain data for plotting the dose response relationship on heart rate.

Left atria. Since there is no spontaneous pacemaker activity, the left atria is electrically stimulated at a fixed rate of 120 beats/min, and in this preparation the effect of the given drug on the force of contraction of the heart (cardiotonic activity) is investigated. Here again, the response to the control drug, isoproterenol is first obtained, followed by 2-3 washes, and then the effect of the drug under study is determined at 5 min

intervals in increasing concentrations, unless the duration of action of the drug is long, in which case we must wait for an adequate time until the original force of contraction has returned to the baseline. The main advantage of using the paced atria is that the indirect effect of a change in rate on the cardiac contractility is eliminated by keeping the rate constant by electrical pacing. Thus, each drug must be independently examined on the rate (right atrium) and force (left atrium) of contraction.

Observations. In view of the limited time available, it was decided to first establish the technique and then if time permits, to test the effect of one or more of the Thai plant extracts described above. In very preliminary experiments, it was only possible to test a very limited dose range of the extracts.

However, some very interesting results were obtained with the extract of Nelumbo nucifera, which produced an increase in the force of contraction but no change in the heart rate. The positive inotropic action was seen with concentrations as low as 0.5 ug/ml. This was the most exciting observation, since to our knowledge, no report in the literature has described the selective positive inotropic action of Nelumbo extract on the heart. This observation must be confirmed and extended further in the next several months, and the detailed effect of various concentrations must be examined in this laboratory. It also needs to be established which of the known active principle has the cardiotonic activity, and to study the structure-activity relationship. All of these experiment have been outlined and will be performed by Mrs. Pattama and her colleagues in constant advisement of the results with me by correspondence before my next visit under this project.

The results with other drugs are summarized in the table below:

DRUG	HEART RATE	CONTRACTILITY
Solvent(ETOH)	no effect	no effect
Isoproterenol	increased	increased
Terpinen-4-ol	no effect	decreased
Tween-80	no effect	no effect
Tinospora	no effect	no effect
Ginger oleor.	no effect	increased*
Garlic natura	sl decrease	sl decrease
Cyperus rotun.	no effect	decrease

* tachyphyllaxis was noted with the next dose.

IV. SCREENING FOR ANTIANGINAL/ANTIHYPOXIC ACTION

Experimental preparation. The isolated guinea pig left atrium paced at a constant rate of 120 beats/min as described above was utilized in this experimental model to test the potential antianginal/antihypoxic activity of the Thai natural products. Since the screening of the coronary vasodilator activity of various drugs can be tested in the isolated Langendorf heart preparation, which is a well known technique, and can be tried at PNPD later, it was decided that the effect of the plant extracts may be better evaluated in a new model of myocardial hypoxia. This preparation was demonstrated in the laboratory by setting up the left atria as described above. After stabilization of the preparation, hypoxic condition was induced by replacing oxygen with 100% nitrogen which was bubbled through the tissue bath. This procedure resulted in a gradual decline in the force of contraction over the next 10 min. The hypoxic condition was maintained for the next 10 min when nitrogen was replaced by oxygen, which resulted in a gradual restoration of the contractility of the atrium.

A major argument in justification of this technique to study the effect of various plant extracts is that while a pure coronary vasodilator activity is not presently considered as the only mechanism of antianginal action, this model may screen a true antihypoxic action of the plant material, even though the drug may have a minimal coronary vasodilator action. A potentially beneficial effect of the extract on tissue metabolism, membrane stability or some other action (i.e. effect on intracellular calcium accumulation) in presence of hypoxia would be screened in this model.

Protocol. The following experimental protocols will be performed to screen the plant extracts in this model.

1. Effect on the rate of decrease in contractility. The decline in the rate of contractility will be established by measuring the developed force at 1,2,5,7.5 and 10 min after the exchange of oxygen by nitrogen, and plotting the time course of this decline in control and drug treated preparations. The drug under investigation would be added to the tissue bath 10 min prior to inducing hypoxia.

2. Effect on the rate of recovery of contractility. In this protocol, the rate of recovery of developed force after a fixed period of hypoxia (20, 40 or 60 min) will be measured by recording the force during the recovery period after oxygenation has been restored. The time course of the rate of increase in developed force, as well as any increase in the resting tension (contracture due to intracellular accumulation of calcium ion or other substrate during prolonged hypoxia) will be plotted in control and drug pretreated or treated (adding the drug after induction of hypoxia) preparations.

V. ANTIARRHYTHMIC ACTIVITY

Although time did not permit to actually demonstrate the technique for screening of the antiarrhythmic activity of the Thai traditional drugs, especially in view of a lack of sophisticated instruments, e.g., even a simple two channel stimulator, details of the screening procedures for future use were discussed. A very simple screening test is to study their action on the relative and effective refractory periods in the isolated guinea pig atria, a technique already established here. The other screening method is ventricular fibrillation induced by barium chloride in mice. Both these screening methods will be demonstrated during the second phase of my mission.

VI. STEPS NECESSARY TO DEVELOP A DRUG FROM INITIAL SCREENING TO THE FDA APPROVAL

Several sessions were held with the staff of PNPD to review the general requirements of the FDA on the pharmacology and toxicology of a new drug, including possible mechanism(s) of action, before clinical trials are permitted. Brief details of the process necessary for the approval of the Institutional Review Board (IRB) before starting the clinical trials were discussed.

PROPOSED ACTIVITY FOR THE NEXT 12 MONTHS

Screening for the cardiovascular activity. Experiments will be continued in anesthetized Wistar rats for screening of the antihypertensive activity as described above. At least three to five doses of each new plant extract will be injected intravenously at 10 min intervals after an initial response to a control dose of adrenaline shows that the preparation is stable. Screening for the cardiotonic action will also continue in the isolated guinea pig atria as described above.

If any plant extract shows an antihypertensive action, an appropriate dose of this drug will be selected for additional experiments to determine the maximum response as well as the time course and duration of antihypertensive action. Similarly, further experiments will be performed for drugs with cardiotonic, antianginal or antiarrhythmic activities. The following additional plants have been recommended for these experiments, the priority of their testing to be determined by their availability and literature review:

1. ACANTHUS ILICIFOLIUS
2. ALPINIA CHONCHIGERA
3. A. GALANGA
4. ANDROGRAPHIS PANICULATA
5. CEREBERA MANGHAS

6. C. OLOLLAM

7. DRYOBALENOPS AROMATICA

8. ERIOBOTRYA BENGALENSIS

9. HYOROPHYTUM FARNICARIUM

10. MANSONIA GAGEI

11. MUSA SAPIENTUM

12. OCHROCAPUS SIAMENSIS

13. PANADUS ODORUS

14. RHEMANIA GLUTINOSA

15. STERCULIA LYCHNOFORA

16. TINOSPORA TETRASPERMA

17. UNCARIA FERREA

It may be pointed out that the selection of these plants is recommended (please see the Midterm Technical Report by Dr. Nitya Anand, Dec 9-19,1988) after a careful review of the literature as well as consultation with the Ayurved Vidhayalai, Bangkok.

Detailed antihypertensive actions. Detailed antihypertensive activity of the following drugs which were identified to lower blood pressure in preliminary screening (see above) will be performed to confirm and extend the dose response relationship, duration of action as compared to the vehicle control:

Tinospora crispa L.
Nelumbo nucifera
Garlic natura
Odorless Garlic natura
Garlic oil as well as its solvent

Oral activity of these drugs also need to be established in further experiments. After performing these experiments, appropriate statistics will be applied to the results.

In case of Tinospora, attempts should be made to perform chemical identification of the active principle(s), since the extract is known to be composed of many alkaloids, and other substances. The antihypertensive activity of the pure chemical components of Nelumbo nucifera also needs to be tested.

After these experiments have been completed, detailed studies on the mechanism of antihypertensive action of these drugs will be necessary, and these may commence by October 1989. A comparison with standard drugs with known mechanism of action(s) will also be made at this time.

Detailed cardiotonic actions. Preliminary results with the extract of Nelumbo nucifera suggest that it has a cardiotonic action. These observations need to be extended further in the following series of experiments:

a. Detailed concentration-response relationship,
b. Effect of prolonged exposure on the cardiotonic action,
c. Effect of different concentrations on heart rate,
d. Possible mechanism of action, including comparison with drugs with known mechanism(s), e.g. digoxin or catecholamines.

OTHER ORGANIZATIONS VISITED AND SCIENTISTS MET

1. Chulalongkorn University.

Dr. Prasant

I visited the School of Pharmacy, and met with the Faculty and staff of the Department of Pharmacology. They have an excellent laboratory facility, and the main interests in research appear to be in the areas of cardiovascular and neuro pharmacology. Dr. Prasant, chairman of pharmacology had been working with a new drug from the plant source, and has reported it to be a non selective calcium channel blocker. He also is a consultant to TISTR, and this arrangement is very helpful and should be maintained.

2. Government Pharmaceutical Organization (G.P.O.)

Dr. Thaharn Bhubhand, Director
Miss Panida Kanchanapee, Associate Director

General discussions were held about the policies regarding drug development in Thailand, their marketing interests, and their interest in the natural products for cardiovascular diseases. At present, G.P.O. is developing the following drugs from natural sources:

Endographoli
Cassialate*
Aloe*
Balaria
Curcuma longa
Garlic natura*
* these in collaboration with TISTR

They also have other products in various stages of research and they will be explored further in due course of time.

3. Mahidol University, Faculty of Science.

Jutamaad Satayavivad, Ph.D.,Chairman
Udom Chantharaksri, Ph.D.

I met the faculty and staff in the department of pharmacology, and gave a talk to them on the role of cholesterol in cardiovascular diseases. Dr. Jutamaad is doing work with isolated atrial preparation, and her main interest is to study the regulation of receptors during chronic drug therapy. Dr. Udom is interested in the drug therapy of thalessemia which is very common in the Thai population.

4. Siriraj Hospital, Division of Cardiology.

Dr. Narimul Charoenchob

Siriraj Hospital is the largest Government Hospital in Thailand, with approximately 2000 beds. It is the teaching Hospital of Mahidol University School of Medicine. Their Cardiology Division has 6 very well trained cardiologists. The facilities in their Division are very modern, and their CCU is also very well organized along the same lines as in the U.S.A. They are using almost all modern drugs (including tPA which is still experimental in Thailand). Their practices are about the same as in teaching hospitals in U.S.A.

I had a very frank discussion about clinical pharmacology of cardiac drugs, and it was my general impression that clinical trials may be possible at Siriraj Hospital with Thai traditional medicines after all the necessary pharmacological and toxicological work has been completed.

5. National Institute of Health.

The present building of The National Institute of Health is a very modern building which was a gift of the Japanese Government. The major interests are in the areas of virology and epidemiology. Their pharmacology department is interested in natural products, but their major emphasis is for Thai traditional medicines for use in community Hospitals. There is a very well furnished cardiovascular laboratory, but the work is mostly to test the safety of the natural products for other uses. In one experiment, a 1gm/kg dose of the extract of the drug was used, and the drug had a weak antihypertensive and femoral vasodilator action.

CRITIQUE AND RECOMMENDATIONS

This is my first exposure to TISTR and their PNPD, and from the reports of an excellent progress made in the past and my own personal observations it is clear that a very impressive array of important contributions have been made. Since there is so much renewed world wide interest in the natural products, every effort should be made to continue this very important work. We all know very well from previous experiences with modern drug discovery that an immense amount of concerted effort must

be maintained for many years before a drug can be brought to the market for general use. It takes many painstaking years to assemble a very well trained team of scientists in several fields to work together on drug development, and now that this team is in place in PNPD at TISTR, their combined efforts should bear fruit when new products from the Thai traditional medicine are ready for clinical testing in treatment of cardiovascular diseases.

My visit to many other important Scientific Institutions in Thailand also convinced me that there is no other place here where the scientists are carrying out a systematic screening of all natural products which may have significant cardiovascular or immunomodulator activity based upon a long history of traditional use in Thailand. Scientists in the Universities are much more interested in investigating the mechanisms of actions, whereas those at the National Institute of Health are more interested in developing drugs which may benefit the community hospitals in the rural areas. In this context then, the dedicated interest of the entire team lead by Mrs Sasithorn Wasuwat at PNPD and the training and experience the staff has now received over the last several years suggests to me that every effort must be made to continue this very important task. Since there are many more plants that have been identified as having potential activity, but have not been screened as yet, much work still needs to be performed in future. This assessment also reflects a limited degree of coordination to screen drugs from the Thai traditional medicine.

Technical staff. The present technical staff in pharmacology is well trained in general pharmacology, and I found them to be very competent and hard working. Several members have also received specialized training abroad to enhance their competence in various aspect of drug development and this must be continued. In addition, the present team should be designated for "cardiovascular drug development" since they have now learned special skills in the last two months and there are at least two exciting drugs that need to be thoroughly investigated. The present three members of the team (Mrs. Pattama, Miss Chuleratana, and Miss Tuanta) will be very busy in detailed cardiovascular work up of the two promising leads (Nelumbo extract, and Tinospora extract) and they may find it difficult to continue screening new drugs in their laboratory. Screening of the Thai plants identified above (see p 10-11) may be assigned to two new technical staff members who should be hired as soon as possible, and their full responsibility would be to continue screening for the cardiovascular activity of new drugs.

Facilities. Facilities for screening cardiovascular drugs are at a bare minimum, and unlike other similar institutions in other developing countries such as CDRI, Lucknow, India and most drug companies, only one drug in one animal can be screened per day. There is also no provision to test the oral activity of any drug in unanesthetized animals. Once the screening phase is over, a lot more sophisticated cardiovascular work up would be necessary to provide detailed information on the activity of the selected compound in a variety of experimental animal preparations. For example, once a drug is found to lower blood pressure in normal rat screen, further experiments will be necessary to test its activity in various experimental models of hypertension. Plans should be made now to prepare for this expanded work load in the very near future, since it often takes 1-2 years before the

instruments arrive and the personnel can be fully trained. I shall define the needs for instrumentation into the following categories:

Immediate needs: The following instruments are required to continue the present pace of screening activity and additional work up of currently identified drugs on the cardiovascular system:

a. Additional blood pressure transducer,
b. Additional force displacement transducer,
c. A complete system for measurement of tail blood pressure in conscious rats

These items are needed as soon as possible, since at present, with only one polygraph, and only one transducer, it is possible to run an experiment only with either the right or the left atria at one time. This really is very difficult, since the guinea pig is sacrificed in the morning when both the atria are isolated, but the experiment with the second atrium does not begin until the afternoon. This is unacceptable for technical reasons. It would be a lot easier with two FT-transducers to run both atria at the same time. Similarly, with two blood pressure transducers, two pressures can be monitored simultaneously, which will be required when the effect of these drugs need to monitored on the systemic and cardiac pressures simultan-eously. At present there is no technique available here to be able to investigate the oral activity of any of these drugs on blood pressure of conscious animals,and therefore item listed in c. above would be most desirable not only for screening of several new drugs simultaneously each day but also to study the oral activity as well as duration of action of those drugs already identified with cardiovascular activity.

Needs within the next two years. A well equipped cardiovascular laboratory should be organized with necessary instrumentation to be able to perform all secondary experiments for additional work up of the drug identified to have the desired activity from the initial screening program. This would include experiments to determine the mechanism of action, effects on the cardiac contractile force, coronary blood flow and other regional blood flows in large animals (such as dogs). A very basic laboratory should therefore include at least the following equipment:

a. an eight channel recorder with monitor scope, with appropriate amplifiers for pressure, EKG and flowmeters
b. one large animal respirator,
c. one blood flow monitor with necessary sizes of flow probes
d. one thermodilution cardiac output instrument,
e. instruments for surgery, including operating table, cautery, instruments for open heart experiments, strain guage arch etc.
f. one two channel stimulator with stimulus isolation unit to run trains of extrasystoles.

I strongly recommend that steps be taken now to begin necessary process to procure the above equipment as soon as possible.

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