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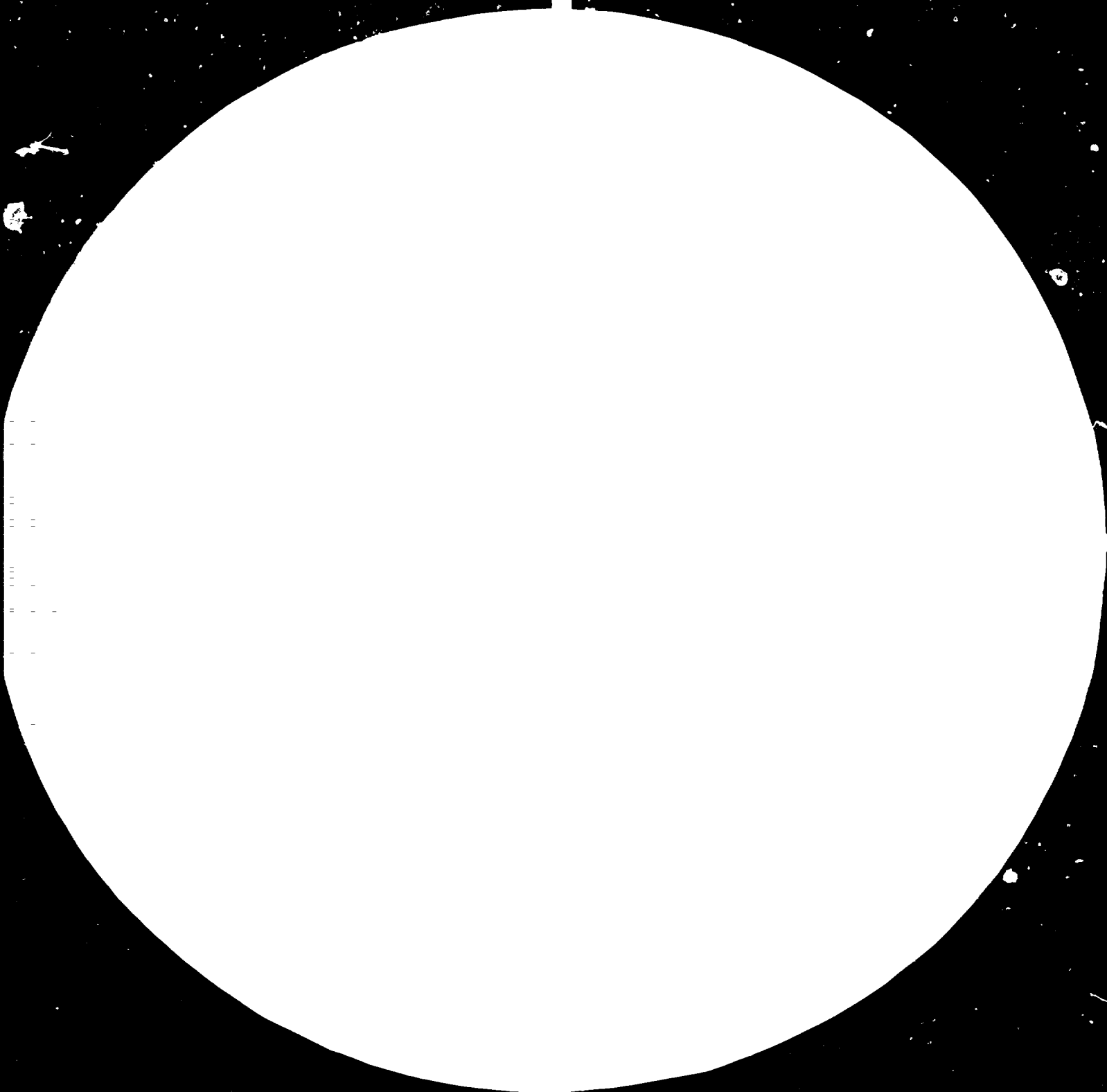

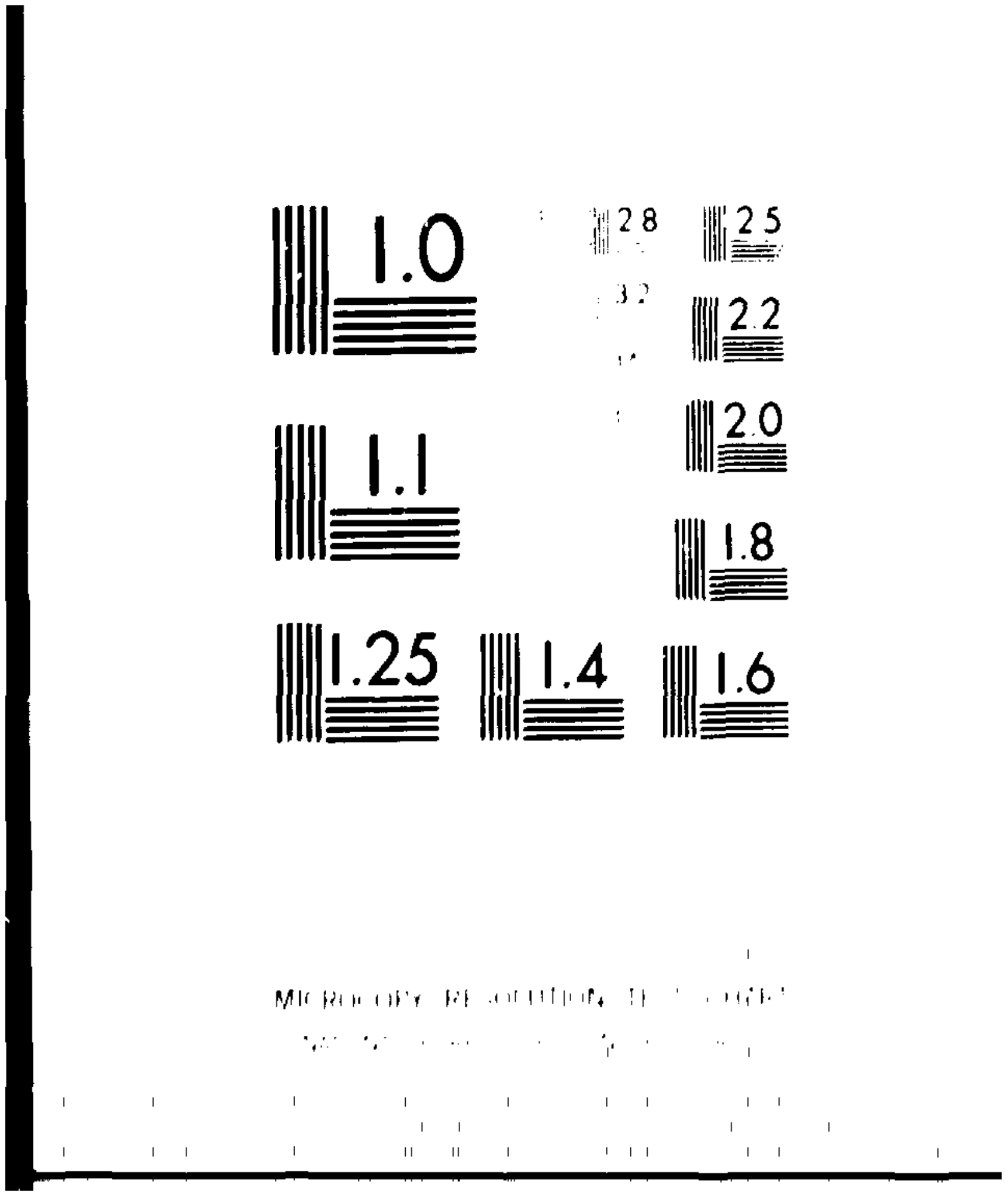
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DP/ID/SER.A/405

10 December 1982

English

Nepal.

STRENGTHENING THE ROYAL DRUGS RESEARCH LABORATORY.

DP/NEP/80/003

NEPAL

Technical Report *

Prepared for the Government of Nepal

by the United Nations Industrial Development Organization,

acting as executing agency for the United Nations Development Programme

Based on the work of Prof.Finn Sandberg

Consultant in the Production of Pharmaceuticals from Medicinal Plants

United Nations Industrial Development Organization

Vienna

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General

Mr.Wijesekera's decision to make a split mission for this post has shown to be fruitful.During the first period (April - May 1982) the job was to start from scratch, and one of the main task was to make an adequate equipment list.

In the time period between first and second stay in Nepal the Project Co-ordinator Mr.J.G.Meredith, has arrived and his main task will be the establishment of the pilot plant in Godawari. The consultant could therefore concentrate on the activities in the laboratories in Thepathali.

Equipment list

The list brought by the consultant to Vienna in May 1982 has been divided into four categories and part of the equipment is ordered. The ramaining items have all been put into a complete list of priority:

1. Category I - Processing Crude Herbs

Priority order: (1) item 18
(2) item 14
(3) item 15
(4) item 19
(5) item 17
(6) item 13
(7) item 16

2. Category II - Formulations for making single dosage forms

Priority order: (1) items A1-10, (2) items B1-6 and E, (3)items C1-3, (4) item D7.

3. Category III - Laboratory Apparatus

Priority order: (1) item 5, (2) item 3, (3) item 4, (4) item 7, (5) item 2.

4. Category IV - Pharmacology Equipment

Priority order: (1) item 16, (2) item 8, (3) item 9, (4) items 15, 17-21 (5) item 22, (6) items 10, 23, 12 (7) items 11, 13, (8) item 14.

Priority order between the categories:

1. Category IV
2. Category III
3. Category I
4. Category II.

This list was immediately cabled to Dr. Wijesekera and the cost will be borne by budget line 49.00 of the project under 1982-1983.

Comments

It was apparent at the discussion in October with the expert in microbiology Mrs. Margaretha Cordes, that the equipment in the section of microbiology is poor and is not at all adequate for any fermentation work. When the present list of equipment list was made, evidently the needs for microbiology were overlooked.

However, Mr. Meredith will look for other possibilities of financing - possibly Overseas Development Corporation, U.K. - such equipment and Dr. Cordes got the task to prepare a list of necessary equipment for Mr. Meredith's consideration.

STAFF (PROJECT PERSONNEL)

1. Production Technologist (Post 11-01)

Mr. J.G. Meredith started his assignment 1st August 1982 and will terminate 1st February 1984. Although his arrival from the project point of view was somewhat too early, his period in Nepal will be sufficient owing to the planning progress made by the excellent A.D. Shrestha, senior scientific officer.

It is foreseen that the first equipment from Tournaire, Grasse, will arrive around middle of 1983 when the corresponding building will be ready.

Mr. Meredith has now his office at Thapathali, but a little site office is already erected in Godavari; to be used when the work require a daily stay at the site.

It can now be foreseen that Mr. Meredith will have several months to run in the equipment and make an on-the-spot training of personnel.

2. Pharmacologist (Post 11-02)

Dr. Patrick Williams has been visited in London by the consultant and he will be revisited in the end of October after inspection of the conditions in the laboratory and animal house in Thapathali.

As regards localities the new acquirements are:

(a) the pharmacological screening will be performed in a separate quiet room in the same floor as the animals are stored. Enough benches will be provided.

(b) the Grass - instrument will be installed in the present Biochemistry laboratory where Dr. Williams also will have his writing desk. Concerning the necessary breeding of rats, this has already started on a moderate scale

with the albino rats of a strain from CDRI, Lucknow. New cages have been ordered locally.

Dr. Williams will devote his time to:

1. guide the pharmacological screening of plant extracts on rats and when positive (therapeutically promising) results are obtained, coordinate a profound study of that particular plant together with the analytical chemist and microbiologist.

2. install and run in the new equipment, especially the Grass polygraph with accessories.

3. work out suitable in in vitro test for monitoring the purification of plant extracts.

4. train the nepalese personnel in bioassay and its statistical application.

5. guide the breeding of animals, especially rats and together with the caretaker keep up-to-date records of the animals.

3. Expert in Economic Mapping (Post 11-03)

The deadline for the previous expert, Mr. Bojor from Roumania, expired 1st October 1982. Therefore a new candidate has to be found.

It is agreed upon by all parts involved that the expert in economic mapping should first of all concentrate to find the areas in Nepal, which from various aspects are suitable for large scale cultivation of medicinal plants. The duration of this post is supposed to be limited to 8 months.

4. Analytical Chemist (Post 11-04)

There were two applicants, both well qualified. Of the two, Dr. Jan Karlsen, Institute of Pharmacy, University of Oslo, has been chosen. The

consultant knows him since several years and can varify that he is an excellent man. Of special interest is his experience in the field of essential oils.

The consultant has proposed Dr. Wijesekera, that Dr. Karlsen passes Uppsala on his way to Vienna for discussions and informations.

Dr. Jan Karlsen will devote his time to:

(i) work out the analytical method for determination of the content of pharmacologically active component(s) in plants of interest.

(ii) participate in the purification of those plant extract, which has shown a positive effect.

(iii) In the field of essential oils: (a) perform gaschromatographic and other analysis of oils that HPPC produced on experimental and production scale (b) assist in the organoleptic evaluation that the expert in microbiology will perform.

5. Microbiologist (Post 11-06)

At the end of the consultant's stay in Kathmandu, (May 1982) Dr. Margaretha Cordes visited the Royal Drugs Research Laboratory and showed her qualifications as microbiologist. She had a good background and experiences from Central America. Therefore she was proposed for a six months assignment. It should hopefully start in October.

Dr. Cordes will devote her time to:

(b) be the acting head of the microbiology laboratory when Mr. P.M. Shakya is sent for training to Hindustani Antibiotics, Puna.

(ii) perform the microbiological screening on the same plant extract that Dr. Williams is testing on rats. The screening should involve;

i. anthelmintic on earthworms.
ii. test the inhibitory effect on Shigella.
iii. test on the inhibitory effect on Entamoeba histolytica.
iv. test on antifungal activity.

(iii) organise an organoleptic laboratory which should primarily serve the evaluation of essential oils.

(iv) carry out the microbiological test samples that are sent to Royal Drugs Research Laboratory through the Drug Act.

6. Consultant in Production of Pharmaceutical from Medicinal Plants (Post 11-51)

The work of the consultant has been useful for the start of the project. It is proposed that 1 month is given in 1984 (taken from the expert in economic mapping) to make a follow up and final evaluation.

7. Associate Expert/Economist

Mr. Joe de Boeck will serve for a year (15 march 1982 - 15 March 1983) and his work has been very useful so far.

It was agreed upon that Mr. deBoeck should devote his time to cost/benefit studies for the following drugs:

(a) Belladonna
(b) Pyrethrum
(c) Rauwolfia serpentina
(d) Citronella oil
(e0 Palmarosa oil
(f) Lemongrass.

It would be of great importance to evaluate the harvest of 1983 (from May to June) in order to obtain more reliable figures for the production costs than those for 1982. It is therefore proposed that Mr. deBoeck will obtain a

prolongation of 3 months (taken from the expert in economic mapping).

Since the prices for the products manufactured by HPPC generally are higher than the world market price, Mr. deBoeck should particularly look for the weak point in the cultivation/production sequence in order to reduce the costs.

FELLOWSHIPS

The training programme for 1982 comprises quality control and has been handled by WHO. The money required, US$ 52,771 has been transferred.

However, WHO has been extremely slow in handling this matter and the promises given to me by Dr. Parera have by no means been kept. In May, 1982 it was decided that four (4) staff members should go in June and four (4) in November (Appendix I). The first group has not yet left Kathmandu. The project co-ordinator has to exert a constant pressure on the responsible authorities to speed up this training programme.

Concerning the fellowships for 1983/84 (US$ 130,000 + 50,000) they are fortunately enough handled by UNIDO and Royal Drugs Research Laboratory. A complete priority list is worked out for both years (Appendix II). The accumulated cost for the candidates in the order will determine if the whole programme or only part of it can be performed.

The duration of some training programmes might also be diminished in order to cover as many activities as possible. "New candidate" means a new staff member that will join the Royal Drugs Research Laboratory in due course.

WORK PLAN

A workplan will be given for:

1) the scientific activity at RDRL.

2) the establishment of a pilot plant in Godawari.

A. The Scientific Activity at RDRL

1. Collection, Extraction and Screening of Plant Materials

The supply of plant extracts for the joint screening on rats (Dr. Williams) and microbiological tests (Mrs. Cordes) has been discussed, and the following points were agreed upon:

i. The principle for collection of plants for screening will be the use in the local folklore medicine: information should be obtained from the local population, i.e. inventories should be carried out in various parts of Nepal.

In the inventories collecting numbers, good herbarium specimen, part of plant used and how the plant is used therapeutically must be noted.

A second source of information is the Ayurvedic scripts.

ii. Responsible for the collection of enough plant materials is Dr. P.R. Shakya (Godawari). When other staff members make an excursion for collection of specific plant materials (for instance Aconitum-species), they should always ask the local population for their use of plants and make acollection accordingly.

iii. It is envisaged that during the stay of Dr. Williams about 100 species should be screened.

iv. Responsible for the preparation of plant extracts is Mrs. Sumitra Vaidya.

v. The solvent should be 50% ethanol.

vi. The extracts will be suspended in 1% Acacia or ¼ Agar solutions.

vii. First a rough LD50 - i.p. on mice is performed. Then ¼ of LD50 is given i.p. to rats for the screening according to Malone (modified by Sandberg). If possible one lethal, three active and one non-active doses are given.

viii. When a positive (therapeutically useful) effect is verified on 3-4 animals at least two doses, the crude extract is treated in a liquid/liquid extractor with: (a) petroleumether, (b) ethyl acetate, (c) methanol (d) water. This is performed by Mrs. Vaidya. The four fractions are then screened again.

After discussion with the expert in analytical chemistry also other types of fractionation could be used.

2. Active Collaboration in the Study of Medicinal Plants

The results of the dual screening will be discussed at regular staff meetings.

Items for active collaboration between pharmacologist, phytochemist, analytical chemist and microbiologist are, among others:

i. The follow-up of positive results from the screening of medicinal plants.

ii. In the field of essential oils: for quality control and development of new items the joint efforts of the organoleptic laboratory (Mrs. Cordes), analytical chemist (Dr. Jan Karlsen) and technologist (Mr. Meredith) will be creative.

iii. The therapeutic potentiality of Nardostachys jatamansi will be evaluated.

iv. Valeriana Wallichii, its content of valepotriate in plants of various origin and the preparation of a stable extract is a very important problem for the analytical chemist, botanist, pharmacologist and galenical pharmacist.

v. Glycyrhiza glabra has great export potentiality: its content of glyzyrrhizin and its cultivation should urgently be studied.

3. Regular Staff Meetings

The most important step to be taken in the project is the starting of regular staff meetings, where all research workers mandatory are obliged to participate. Each research workers will give an account of his/her achievement, progress and difficulties encountered. The results will be discussed and minutes are taken, being the starting point for the next meeting to evaluate the research activity.

The regular staff meetings for research will be held with an internal of 3-4 weeks.

B. Establishment of Pilot Plant at Godawari

1. The Technical Problems

These involve the building of the various facilities and installment of the equipment.

The study tour, decided in May, was finally started on 6 th October for a fortnight in India: Lucknow, Baroda, Hyderabad, Jammu. Participants are Mr. A.D. Shrestha (Senior Scientific Officer), Mr. D.R, Tiwari (Engineer) and Mr. M.M. Pant (Architect). Certainly some progress have been made since May, and there are all reasons to believe that Mr. Meredith and Mr. Shrestha will achieve the target set for the installation.

2. The activities

The choice of the plant to be extracted in Godawari will primarily be those that later on will extracted on an industrial scale by HPPC, i.e. as a start belladonna, pyrethrum and Rauwolfia serpentina, Berberis Aristata.

The most important activity, however, is the preparation of various extracts for experimental purpose, for clinical trials etc.

It is envisaged that the 1983-crop of various medicinal plants will be extracted in Godawari.

COORDINATION OF PROJECTS NEP/80/003, NEP/79/007 and NEP/80/044

It is necessary to look at these three projects as a functional unit. Therefore they have been discussed during the consultant's stay in Nepal.

1. NEP/79/007

This project is now signed. Since the executing agency is FAO in association with UNIDO, Dr. Malla has the definite opinion that UNIDO propose to FAO a suitable candidate for post: Chief Technical Adviser, Agronomist (3 man/year). Needless to say it is of utmost importance for the success of the project to have the right man.

1. Dr.J.E. Parleviet
   Institute of Plant Breeding
   Laureksa Allee 166
   Wageningen
   Netherlands

2. Mr.E.H.D.Smit
   Netherlands

3. Mr.E.V.G.Nair
   India

Mr. Parleviet has been 4 years in Kenya for the cultivation of Pyrethrum and has also made a study on Pyrethrum - cultivation in Nepal. He has given a very solid impression, and is fully recommended by Dr. Malla and his co-workers. He should be contacted by telephone when the consultant is in Vienna.

As regards the marketing consultant (3 man months), Mr. Meredith has shown that the Interdisciplinary Research and Consulting Company, D 7108 Moeckmuehl, West Germany (IFB) has highly qualified staff memoers for marketing and thus he proposed that IFB should be contacted for a suitable candidate. (vide also addendum)

It should be mentioned here that a lot of preparatory work for the cultivation has already been by Mr. W.J. deBoeck. His report "Cultivation, Processing and Marketing of Belladonna by HPPC" (Appendix III) is valuable in this respect as well as "A report on extending Medicinal and Aromatic Plants in Public Sector" compiled by G. Amatya (Appendix IV).

2. NEP/80/044

This project has been discussed in a meeting with Mr. Meredith, Mr. deBoeck, Dr. Asfaq Sheak (General Manager of HPPC) and the consultant.

As regards the equipment list, Mr. Meredith has written to Dr. Wijesekera on 15 September 1982, and what is needed is now a more precise estimate of cost (through Tony O'Connell) to see if the allocated US$ 600,000 is enough.

Concerning the project personnel it was agreed that the consultants (12 m/m) can be totally omitted or substantially reduced. Furthermore the role of a FAO-consultant was highly question, since this project is a technical one, not agricultural.

The post as Project leader/Production Manager was not discussed on the level of suitable candidate, but it is the consultant's opinion that Mr. Meredith would be a suitable candidate.

The proposed post agro-industrial economist/marketing specialist (18 m/m) was proposed - after elaborate discussion - to be changed to Economist/cost-benefit analysis. After extensive discussions the consultant is convicced that Mr. Joe de Boeck would be very suitable candidate with his accumulated experience in this type of work, the conditions in Nepal and his great interest in the project.

Seen from situation in the field it as urgent that the project document will be finalised and signed.

The counter-part for NEP/79/007 and NEP/80/044 is Dr. Asfaq Sheak (General Manager of HPPC), who is a knowledgeable, reliable and creative man with great enthusiasm for the projects, so UNIDO has all reasons to be optimistic for these projects.

As regards the sites, where the UNIDO equipment will be installed, the soxhlet extraction unit will be placed in Koteshor (near the airport of Kathmandu) and the steam distillation plant in Tamagari, 150 kms from Kathmandu.

Dr. Sheak demonstrated the site in Koteshor and the impressive planning: lay out and construction of building that the DOME consultancy Co. has carried out.

The construction work will start in two months' time.

Dr. Sheak has started his marketing contacts, supported by Mr. deBoeck's information obtained from his visit in Bombay.

The British Company Andard - Mount, 24/28 London Road, Wembley, Middlesex HA9 7HA, is a costomer of Belladonna extract, provided the extraction method given by the company, is followed.

For Pyrethrum there is good potentialities in India and for local use Mercantile Co., Kathmandu will be a customer.

RESUME

With the exception of some unnecessary delay in a few cases (the cars, WHO fellowships, study tour), the initial difficulties have been overcome, definite progresses are made and there are good reasons to believe that the three projects will be carried out successfully.

Addedum to

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DP/NEP/79/007
As a second candidate for the post: Chief Technical Adviser (3 m/m) the following candidate is proposed:

Dr.E.V.G. Nair
Senior Agro-Scientist
International Institute of Ayurveda
P.B. 3871
Trichy Road, Ramanathaparan
Coimbatore 641018
India

Dr.Wijesekera has met him last year at the Lucknow Workshop on Essential Oils . He has presented his CV and the list of publications.

As regards the marketing consultant (3m/m) the ideal candidate has been found : Mr. Sundaresh, Chemist, Bombay.
He has already accepted if he is proposed.

Appendix I

Training Programme 1982

Fellowships, Budgetline 31

	Candidate	Training In	Duration in months	Institute
I.	Start in June 1982: Four candidates			
	1. M.D.D. Bhattarai	Drug Analysis	6	Drug Control Laboratory Government of India Calcutta.
	2. Muna Rajbansi	Drug Analysis	12	Govt. Analytical Laboratory, Ghaziabad, Delhi.
	3. M.P.M. Shakya	Microbiological assays	6	Hindusthan Antibiotics, Puna.
	4. Mohan P. Amatya	Bio-assay	6	Hoffkine Bio-pharma, Bombay.
II.	Start in November 1982: Four candidates			
	1. Mr. D.P. Neupane	Drug Analysis	6	Drug Control Laboratory Government of India Calcutta.
	2. Mr. L.K. Vaidya	Drug Analysis	6	Drug Control Laboratory Government of India Calcutta.
	3. Miss Kamala Manandhar	Microbiological assay	12	IDPL Rishikesh, [illegible].
	4. Mr. S.K.G. Joshi	Bio-Assay	12	National Control Laboratories for Biologicals, Bangkok.

Appendix II

Priority List of Training Programme for 1983/84

Priority No.	Candidate	Training In	Duration in month	Place of Training
1	Mr. Khah	Breeding and maintenance of laboratory animals	3	CDRI, Lucknow.
2	Mr. D.R. Shakya	Electronics with special reference to the general maintenance of instruments	6	Chandigarh, Cyprus.
3	Mr. Damodar Shrestha	Mechanics for the maintenance of pilot plant equipment.	6	Suitable workshop, India.
4	Mr. Damodar Nepal	Glass blowing for repair and fablication of laboratory glass apparatuses	6	Suitable Workshop, India.
5	Mr. Mallick	Biological screening tests for hypoglycemic and lipid lowering activities	3	CDRI, Lucknow.
6	Mrs. Sumitra Vaidya	Phytochemistry	12	Dr. Phillippson, the School of Pharmacy, London.
7	New candidate	Pharmacology	12	India/U.K. (CDRI)
8	Mr. Navin Shrestha	Unit operation in the extraction of plant material	6	India/Hungary
9	Dr. K.R. Amatya	Synthetic Chemistry on Δ^3-carene	6	Dr. Wesley Cocker Chemical Laboratory, Trinity College, Dublin, Ireland.
10	Mr. A.D. Shrestha	Visit to Pilot Plant equipment fabricators and their users	2	Europe
11	Dr. P.M. Adhikari Dr. S.R. Adhikari	Study tour to the quality control laboratories (biological and chemical analysis)	2	U.K., Sweden, Denmark, West Germany, France, Switzerland.
12	Dr. S.B. Malla Dr. S.B. Rajbhandari	Observation tours on utilisation of medicinal, aromatic and other economic plants in European facilities	2	Hungary, Switzerland, West Germany, Sweden, U.K., France.
13	New candidate	Breeding and maintenance of laboratory animals	3	CDRI, Lucknow.

Priority No.	Candidate	Training In	Duration in month	Place of Training
14	Mr. M.P. Manandhar	Economic Botany with special reference to the utilisation aspects of medicinal and aromatic plants	3	Missouri Botanical and New York Botanical Gardens.
15	Mr. M.K. Bhattarai	Assessment of wild grown medicinal plants	3	Budakalasz, Hungary.
16	Mr. B.R. Shakya	Synthetic Chemistry	12	India /Pakistan(Karachi
17	Mr. U.N. Pandel	Unit operation in the extraction of plant materials	6	India/Hungary.
18	New candidate	Flower/Perfumery blending using essential oils	6	Place indicated by Mr. Meredith.
19	New candidate	Industrial microbiology with special reference to fermentation technique	12	Place indicated by Mrs. M. Cordes.
20	Mrs. Padma Prajapati	Phytochemistry	12	Department of Pharmacognosy, Uppsala.
21	New candidate	Electronics with special reference to the general maintenance of instruments.	6	Chandigarh/alt. Cyprus.

The Work Plan

Description	1982 M	A	M	J	J	A	S	O	N	D	1983 J	F	M	A	M	J	J	A	S	O	N	D	1984 J	F	M	A	M	J	J	A	S	O	N	D
I. Fielding of Consultants and Experts																																		
1. Mr. W.J. deBoeck	=	=	=	=	=	=	=	=	=	=	=	=	=																					
2. Professor F. Sandberg		=	=				=	=																				=	=					
3. Mr. J.G. Meredith					=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=										
4. Economic Mapping Expert									=	=	=	=	=	=	=	=	=	=	=	=	=	=												
5. Mr. Patrick Williams									=	=	=	=	=	=	=	=	=	=	=	=	=	=												
6. Mrs. Margeratha Cordes									=	=	=	=	=	=	=	=																		
7. Mr. Jan Karlsen											=	=	=	=	=	=	=	=	=	=	=	=	=	=										
II. Training																																		
1. Quality Control through WHO (4 participants)									=	=	=	=	=	=	=	=																		
2. Quality Control through WHO (4 participants)												=	=	=	=	=	=	=																
3. Training in different fields											=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=
III. Pilot Plant																																		
1. Building of Pilot Plant									=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=					
2. Installation and running in of equipment																	=	=	=	=	=	=	=	=