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MEDICINAL PLANTS FOR CURING DISEASES OTHER THAN COMMUNICABLE, TROPICAL AND INFECTIOUS *

by

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I INTRODUCTION

The group of diseases, that is dealt with here, is universal. It occurs in the whole world, not only in the developing countries. Therefore the products produced (crude extracts and pure compounds) can be used both in the developing countries and in the industrialized countries.

One of the following cathegories of plants (i.e. the steroidal drugs, producing diosgenin or solasodine, which are the starting material for the production of gestagens and estrogens for the contraceptives) has a special feature. Their use requires a highly advanced, synthetic technique, that possibly India is able to perform, but as far as I can foresee no other developing country within the next decade.

As regards promotion, development and production of drugs based on medicinal plants one can learn very much from India. This country has shown to a large extent how to utilize its own resources, to economize on foreign exchange in its efforts to become self-sufficient and self-reliant in pharmaceuticals. Furthermore, India has stopped the export of some crude drugs and exports instead a purified extract or pure substances extracted and purified from the crude drugs.

In the following, mainly recognized and well established drugs will be mentioned but it is important to mention that an intensive research must be going on in this field mainly along two lines: (1). The search for new plant sources for a certain substance (e.g. new diosgenin bearing plants) and (2) investigation of the efficiency of folklore medicine, among others the Ayurvedic drugs. Results of this research was presented at the 3rd Asian Symposium on medicinal plants and spices, organized by UNESCO and held in Colombo 6-12 February 1977.

The classification of the drugs used in the following paragraphs is mixed phytochemical-pharmacological. The alkaloids, steroidal drugs and essential oil are each homogenous phytochemical groups, whereas the rest are classified according to therapeutic use. General aspects of the production of crude drugs is included in Appendix 1, which is a survey given by Dr. S.C. Datta in his brilliant lecture at the aforementioned Unesco-sympcsium in

Columbo, February 1977.

II DRUGS TO BE CONSIDERED

A. ALKALOIDAL DRUGS

1. Atropa belladonna and A. acuminata

Origin: The leaves of A. belladonna and A. acuminata.
Therapeutical use: The alkaloid atropine has a very wide range of use as a spasmolytic being a competetive antagonist of the parasympatic nervous system.
Marketing prospects: Worldwide, it is very good.
Form of applications: Tablets (often in combination with a sedative). Solutions, eye drops.
Technology for production: Standard alkaloid extractions.
Comments: The situation for this drug in India is very instructive and shows a promising development. Prior to 1960 requirement of belladonna by the pharmaceutical industry was obtained from the wild growth in India. Because of indiscriminate collection, the plants became more or less extinct by 1958 and belladonna and its alkaloids were imported from Europe. As a result of research and development started by Central Indian Medicinal Plants Organisation at its Regional Centre in Jammu & Kashmir, indigenous technology was developed for the production of both Atropa belladonna and A. acuminata and at present 28 tonnes of dry Belladonna leaves are being produced at the farms of CIMPO in Kashmir. Belladonna extract and total alkaloids are being produced by CIMPO at its factory in Jammu & Kashmir.

2. Berberis species

Origin: The root of Berberis aristata D.C., B. asiatica Roxb. at D.C. and B. lycium Royle. These species grow wild in the Northern part of India, mostly in the Himalayas.
Therapeutic use: The alkaloid berberine is used as a specific treatment for tropical diarrhoea (dysenteria of bacillary origine).
Marketing prospects: Very great market in the tropical countries.

Form of application: Orally as tablets, capsules.
Technology of production: Although these species are growing wild, their cultivation is considered to be easy. The alkaloid berberine hydrochloride is at present produced by several pharmaceutical firms in India.

3. Catharanthus roseus

Origin: C. roseus is now a pantropic species, whereas C. lanceus and C. longifolius grow wild in Madagascar and are also cultivated there at present. The aerial part, mainly the leaves, are used as well as the root.
Therapeutic use: The alkaloid raubasine (ajmalicine), which is extracted from the root, is a vasodilator and used as a hypotensive agent. - The dimetric alkaloids vinblasine and vincristine are extracted from the aerial part (the herb) and are very important for the treatment of leukaemia and Hodgkin's disease, respectively.
Marketing prospects: Raubasine is used in the French, German and Italian market to the extent of 5-6 ton annually. - The company Eli Lilly, Indianapolis, USA, consumes 1000 tonnes per year for extraction of vinblastine and vincristine.
Form of application: Raubasine is given orally in tablets, whereas vinblasine and vincristine are used as injection.
Technology for production: During the last 3-4 years the plants have been collected indiscriminately throughout India and several hundred tonnes of roots and leaves have been exported to Europe and United States. Because of the world's interest in this drug, research work has been conducted in CIMPO at its Centre in Bangalore and agro-technology has been developed for profitable cultivation of this plant throughout the country. At present about 500 hectares of land is under cultivation in Southern States.
It is estimated that about 500-600 tonnes of roots are being exported from India annually. Indigenous technology for production of total alkaloids of the roots has been developed and efforts are being made to stop the export of roots and to produce alkaloids in the country itself. The economics of production in India is calculated as follows:

Estimated expenditure for 4 hectares (10 acres) for one year:

		Rupees
1. Preparation of land at 450 rupees per ha	=	1 800
2. Cost of seeds at 500 rupees per keg per acre	=	5 000
3. Raising plants in seed beds	=	200
4. Fertilisers and manures	=	1 500
5. Irrigation	=	200
6. Weeding	=	1 000
7. Harvesting (thrice)	=	3 000
8. Miscelleneous	=	300
9. Extra (unforseen)	=	2 000
		15 000

or 1 500 rupees per acre per year.

Estimated return -

Leaf = 10 tons

Roots = 5 tons

Price of leaf at 4 rupees per kg = 40 000 rupees

Price of root at 8 rupees per kg = 40 000 rupees

80 000 rupees

Therefore profit = 80 000 - 15 000 = 65 000 rupees or a profit of 6 500 rupees per year per acre. (= 800 US dollars)

The plant grows well on loam or sandy loam soils Compact clay loam is however considered undesirable. It also grows on poor laterite soils. It is raised from seeds which are shown in seed beds in spring or summer, March to May, in rows about 2 cm deep and then covered with soil and leaf mould manure and pressed with hand. The seed beds are kept under shade and germination is effected within one week. The plants are transplanted when 7.5 to 10.5 cm in height, at a distance of 30 cm apart in rows 45 cm wide. Application of farm yard manure 3 to 5 ton + di-ammonium phosphate 50 kg + muriate of potash 50 kg per acre is recommended. The flowering starts after about 2 months from the date of planting and continues for 4 or 5 months upto October. Harvesting are started for leaves when the plants are 6 months old and thereafter at an interval of every 3 months. When one year old, the plants are uprooted and the rootscut off. The leaves are dried in the shade and the roots first in the sun and then in the shade.

The roots and leaves have demand in USA, Hungary and W. Germany. The present price of roots is reported to be about £ 1 per kg.

Raubasine as such is present in the root or in the stems in practically very low quantities. Raubasine is obtained in practice from Serpentine, which is the principal alkaloid, through catalytic hydrogenation at an alkaline pH or through reduction with $NaBH_4$. The catharanthus root can be extracted with methyl or ethyl alcohol; the alkaloids can in this case be concentrated with ion-exchange resins, re-eluted and reduced with $NaBH_4$ or Raney's nickel under pressure. In the root alongside Serpentine the isomer alstonine is present, in many drugs in about the same ratio and likewise convertible by reduction into the corresponding tetra-hydroderivative. The end-products may be separated after reduction either by fractional crystallisation or by chromatography on alumina unless the process used foresees a serpentine-alstonine separation by means of salts of different solubility or re-elutions from the columns with appropriate buffers. There are some process and activity patents on tetrahydroalstonine but, as far as I know, there are no important uses for this product, at least on the European market.

A very important contribution to the synthesis of the dimeric alkaloid vinblastine has been made by Dr. Atta-ur-Rahman, H.E.J. Postgraduate Institute of Chemistry, University of Karachi. He has succeeded in synthesizing the dimeric vinblastine from its two monomers, catharantine and vindoline employing a modification of the Prevost reaction and some further steps. Vincristine is obtained from vinblastine by oxidation. Since the two monomers occur in the plant in much higher content than the dimers, there is a good possibility to make vinblastine considerably less expensive than it is at present, provided the industrial method for extraction of these two monomeric alkaloids is worked out.

4. Cephaëlis ipecacuanha

Origin: C. ipecacuanha grows wild in the undervegation in the forest of Matto Grosso-region, Brasil. This plant was first introduced into India by Anderson, the then Superintendent of

Royal Botanical Garden, Calcutta, in 1866, from Kew Gardens. The cultivation was initially experimented at Cinchona Plantation in Sikkim and Darjeeling. Experiments were also undertaken at Nilgiri Hills. Commercial plantation was started in Mongpoo and Rongo Hills early in the 20th century. However, large scale cultivation was taken up only after successful experiments were carried out by Biswas and his co-workers in 1938. Soon after plantations were extended and India became one of the important exporters of Ipecac roots and emetine. At present India produces approximately 9-10 tonnes of dry roots annually.

Therapeutic use: The ipecac root is used in low doses as an excellent expectorant. In high doses it is emetic. Its main alkaloid, emetine, is used as emetic drugs in the case of poisoning and also for the treatment of amoebic dysentery.

Marketing prospects: India produces 9-10 tonnes of dry root annually. If the developing countries will start a treatment of amoebic dysentery, where it is endemic, (e.g. Bangladesh and other countries), the requirement of emetine is almost unlimited.

Form of application: As expectorant and emeticum the crude extract is administered orally. For amoebic dysentery emetine is given as injection (sometimes together with low dose of strychnine).

Technology: Both cultivation and production of emetine is carried out in India. The yield of emetine is increased by metylation and hydrogenation of the minor alkaloids.

5. Cinchona species

Origin: Cinchona was introduced in India by Markham (1859-60), in Nilgiris and West Bengal. Actual plantation was established by Melver (1860) in Nilgiri and by Anderson (1909) in West Bengal. As a result of research work carried out by the British scientists a sizeable Cinchona industry was established in India by the end of the 19th century and India became one of the major producers of Quinine salts. However, because of considerable decrease in demand of Cinchona alkaloids and sharp prices fall in early fiftees, Cinchona plantations in South as well as in North suffered a major set back with the result that the production of Quinine declined considerably. However, due to further increase in the demand of Quinine and Quinidine, the plantations are being extended

and research work for increasing the yield of Cinchona bark as well as Quinine and Quinidine is being intensified.

Therapeutic use: The alkaloid Quinidine is a well known anti-arrhythmic agent, whereas Quinine still holds its position in the treatment of malaria, especially for the chloroquine resistant form. Furthermore its use as a bitter agent in the tonic water and similar drinks is well established.

Marketing prospects: Quinidine is since a decade very expensive and at present approximately 3000 hectars of Cinchona plantations exist in India (state of West Bengal and Tamil Nada) with a production of about 30-32 tons of Cinchona alkaloids annually.
- There are also plantations in Java, Zaire and Central America.

Form of application: The alkaloids Quinidine and Quinine are generally available as sulphate and as remedies they are administered orally.

Technology: Quinidine is basically obtained from Quinine by isomerisation. There are large extraction plants which first isolate Quinine sulfate and then transform it into Quinidine. The drug, treated with alkalis, is extracted by a process of the Rauwolfia type with hydrocarbons and then the percolates are counterextracted with sulfuric acid. Quinine sulfate crystallises from the acid solution. Quinine is oxidised to Quninone, which by subsequent reduction supplies Quinidine and Quinine, separable by optically active salts. The trees yielding Cinchona barks are Cinchona legeriana, C. calisaya hybrids (yellow bark) and C. succiruba (red bark). The usual practice is to uproot the trees when 12 years old and to strip the barks both from stem and root. In some places, coppicing is done and the bark is removed from out branches, allowing the tree to grow and develop new branches. The plants can be grown both from seeds and cuttings.

Growing of Cinchona is at present a profitable industry, well established and details about its economics are available with Cinchona plantations reports published in India and Java.

6. Datura species

Origin: The leaves of D. stramonium, D. metel and D. innoxia, are good sources for extraction of hyoscyamine (the racemic form

is atropine) and scopolamine.

Therapeutic use: The alkaloid hyoscyamine and its racemic form atropine is the most used spasmolytic agent, not yet surpassed by any synthetic drug. As mydriatic agent; scopolamine is nowadays less used than earlier as a strong sedative.

Marketing prospects: In 1976 the price in India for hyoscyamine and scopolamine was about 10 000 rupees per kilo and cultivation of the aforementioned species for alkaloid-extraction appear quite profitable.

Form of application: Atropine and Hyoscyamine is isolated as sulfate and scopolamine as hydrobromide. Both salts are administered orally in tablets, solutions and others. They are also available for injection.

Technology: The drug (bases) can be extracted with acid water at low temperature, the percolates being then neutralised and extracted with a chlorinated solvent. The two alkaloids are separated by counterextraction of Hyoscyamine from the organic phase of pH 6.5 with a phosphate buffer: Hyoscyamine passes into the buffer and is re-extracted after alkalinisation, once again with a chlorinate solvent. By concentrating the final organic phases and treating the residues - with benzene to get Hyoscyamine and with hydrobromic acid to get Scopolamine - the two alkaloids are separated.

7. Glaucium flavum

Origin: Glaucium flavum belongs to the Mediterranian flora and the aerial part (the herb) is used for extraction of glaucine.

Therapeutic use: The alkaloid glaucine is a good antitussive agent, equal in potency as codeine, but has less side-effects.

Marketing prospects: This alkaloid is introduced by Pharma-Chim, Sofia, and has been quite a success as antitussive. It has definitely great chances to be used more extensively.

Form of application: In cough-siroups.

Technology: Standard alkaloid extraction.

8. Papaver somniferum

At present India is one of the important exporters of opium. Poppy is grown mostly in Madhya Pradesh, Rajasthan and Uttar

Pradesh approximately on an area of 54 000 hectares producing approximately 1 300 tonnes of opium annually. Most of this production is exported as raw-opium and only some quantity is converted into morphine and codeine for internal consumption. Recently a large plant has been established in the State of Madhya Pradesh, which will process most of the opium as well as poppy straw and will produce opium alkaloids for export. Morphine and its derivatives are still indispensable drugs. The problem is to avoid its abuse and the illegal production of diacetylmorphine (heroine). One way is to extract the capsules - and not making incisions for collecting the latex (opium). Another way is the genetic developing of strains that contain thebaine and no morphine. Such research is going on in Svalöf, Sweden. The cultivation of Papaver bracteatum, a perennial species, which grows wild in Iran, is tried in pilot plant in several countries. It contains thebaine, which can be chemically transformed to codeine. This synthesis is performed in industrial scale by the pharmaceutical company Weifa, Kragerö, Norway.

9. Rauwolfia serpentina

Origin: Rauwolfia serpentina, which was mentioned as an important drug in the ancient Ayurvedic system of medicine, grows wild in India and has in the last decades been cultivated. The drug consists of the root.
Therapeutic use: The most important alkaloids extracted from the root are reserpine, ajmaline and raubasine, although the last mentioned alkaloid is extracted mainly from the roots of Catharanthus roseus (cf nr 3). Ajmaline is an established antiarrytmic agent, whereas reserpine and raubasine are hypotensive agents; reserpine is also a potent, long acting sedative.
Marketing prospects: To give an idea of their economic importance the figures for the annual consumption on the French, German and Italian market are given: Ajmaline: 7-7.5 tons, Raubasine 5-6 tons, and Reserpine: 300-400 kg. Indigenous technology for production of the Rauwolfic alkaloids has recently been developed in India and the alkaloids needed by the Indian pharmaceutical industry are produced in the country itself.

Form of applications: The alkaloids are used as water-soluble salts for injection and for tablets.

Technology: It grows well in different parts of India under natural conditions and can be cultivated in almost sll S.E. Asian countries. It is propagated from seeds, root cuttings, stem cuttings and even from leaf cuttings. The germination of the seed is low, varying usually from 10 to 50 %. When placed in the water, the viable seeds sink to the bottom and these are used for germination. From root and stem cuttings, 75 % propagation is assured. The plant grows well in soils which are not too sandy or clayey. Application of farmyard manure gives good results. The seedlings are usually raised in the nursery and later on transplanted in the field. The plants require fortnightly irrigation during the hot season and once a month during winter. Roots of exploitable size are obtained from 2,5 to 3 years old plants. About 500 kg of roots are obtained per acre and the market price is about 2.5 US dollar. The roots of this plant are harvested after 2 years, and a plantation of 2 acres, on rotational basis can give a return of 600 US dollars per acre per year. The part of the plant used for extraction is the root or, in the case of Rauwolfia vomitoria, the root bark. The average yields for the three alkaloids are: from 0.5 to 0.7 % for Reserpine; from 0.2 to 0.3 % for Raubasine and from 1.5 to 2.5 % for Ajmaline, with ample oscillations about these figures depending on the area where the plant was harvested and on the secondary alkaloid content. There are many chemical varieties within a given species, obviously indistinguishable on harvesting. Many of these secondary alkaloids are recovered from the water of crystallisation of the principal compounds: Rescinnamine, Reserpiline and α-Yohimbine from the mother liquor of Reserpine and Sarpagine, Alstonine and Methyl Reserpate from that of Ajmaline. All these alkaloids are used successfully in numerous medicinal specialities, either as such or as derivatives.

For producing this range of alkaloids there are fundamentally two industrial methods of preparation, both of which exploit the difference in basicity of the constituents. One selects out the bases in the course of extraction and the other extracts all the alkaloids and subsequently fractionates them in counter-current.

In one case the root is ground finely and treated with a fair amount of water to ensure perfect swelling of the material, which results simultaneously in the breakdown of the cells and to the hydrolysis of the weak bases, that is Reserpine, Rescinnamine, Reserpiline and α-Yohimbine, from the relative natural salts. The drug is conveyed into percolators and extracted with non water-miscible solvents; hydrocarbons have to be used; chlorinated solvents must be avoided because they lead to rapid degradation of the alkaloids. Extraction is continued with fresh solvent until exhaustion of the principal alkaloid. The solvent is then concentrated; the residue can be rendered insoluble in light hydrocarbons and crystallised from ethanol to obtain Reserpine. Rescinnamine, Reserpiline and α-Yohimbine can be obtained from the mother liquor of Reserpine by purifying on alumina or similar absorbents. Obviously for the final purification of each of the last three compounds it may be necessary to resort to salifications with appropriate acids and subsequent crystallisations.

To obtain the other alkaloids present in the drug, the exhaust drug must be treated with aqueous alkalis and re-extracted with the hydrocarbon previously used. Here again the solvent must go for concentration; the residue is crystallised from alcohols. Ajmaline crystallises in high yields through the formation of a crystal of solvation with the alcohol.

The other products can be obtained by processes similar to the ones described for weak bases, although the problem is more complex since Sarpagine is a phenolic alkaloid which oxidises readily and Alstonine is a quaternary ammonium salt. By this method the two fundamental alkaloids can be obtained by direct crystallisation; the drawback is that it involves extracting the drug twice and checking on exhaustion between the two phases.

Another process used involves extracting the drug with a single solvent, which can be an alcohol, acetone, etc., that extracts all the bases simultaneously, counterextracting them, precipitating the total alkaloids and fractionating the individual alkaloids with nonmiscible solvents having different pH values. This type

of process has the advantage of a single extraction and of permitting continous operating; its disadvantage is the number of countercurrent extractions necessary for the separation of the individual constituents, not always devoid of technical snags like the formation of resinous materials, which lead to breaks in the cycles and so forth.

Also other Rauwolfia species are used, above all Rauwolfia vomitoria, which is an bush 2-4 m high in the tropical part of Africa. It is used as a shade-giving bush in coffea and cacao plantations in Africa and is therefore easily available.

10. Secale cornutum (Ergot of rye)

Origin: Secale cornutum (in Latin) or ergot (in English, French) is the sclerotia of the parasitic fungus Claviceps purpurea, developed on the in florescens of rye (Secale cereale).
Therapeutic use: The alkaloid ergometrine is used as oxytocic agent at parturition to deminish the bleeding of the uterus. The alkaloid ergotamine is a sympatolytic agent used to a large extent in the treatment of migraine. The so called ergotoxin group (consists of three alkaloids) is mainly used as a vasodilator.
Marketing prospects: The situation in India is illustrative. About 10 years ago the entire requirement of ergot and ergot alkaloids in India was imported from Europe. After three years of research and development, commercial production of ergot was started in 1968 by CIMPO, Regional Research Laboratory in Jammu. At present India is producing 15-16 tons of ergot annually in the states of Jammu & Kashmir and Uttar Pradesh. The country is now self-sufficient in ergot and ergot alkaloids. In India, the quantity of ergot produced on an acre, is per average 50 kg and at the present price of 70 rupees per kg. The annual return is 3 500 rupees (400 US dollars) per acre. It is a 6 to 7 months crop. For successful production of Ergot with proper content of active principle it is essential that proper strains of rye and ergot solerotia should be used and these have been developed and are being maintained by Central Indian Medicinal plants organisation, in India.

The production of Ergot in some of the S.E. Asian countries can be success and as its demand is very high, necessary attention can be focused on its production.

Form of application: Ergometrine is only used in the injection form, whereas the other alkaloids are administered both orally and parentarally.

Technology: The production consists of two phases; viz (1) Cultivation of the rye plant in the field and inoculating the inflorescens with a spore culture and (2) Production of the spore culture in the laboratory. The rye plant is grown in similar way as wheat crop during the winter months, the seed being sown in India in middle October and the inoculation is done in end of January or early February.

11. Strychnos nux vomica

Origin: The tree Strychnos nux vomica grows wild throughout the Indian plains and Southern plateau and in Cambodia and neighbouring countries. There are also cultivations, in Orissa and other places. The seeds are used for extraction of strychnine and brucine.

Therapeutic use: In low doses strychnine is used as a stimulant in tonics and in injection preparations for instance together with emetine for the treatment of amoebic dysentery. Owing to the very bitter taste these alkaloids are also used technically to denaturate alcohol in cosmetic preparations.

Marketing prospects: Previously seeds were exported from India, but as a result of proper survey, screening and development of indigenous technology the export of seeds has been stopped and strychnine and brucine are now produced in the country and exported to other countries. At present about 12 000 tons of seeds are extracted in India, and alkaloids worth 3.5 million rupees are exported annually. The situation in Cambodya is not known for quite obvious reasons.

Form of application: Strychnine nitrate is the salt commonly used and is given orally in tonics and for injection.

Technology: The Bengal chemical and pharmaceutical works in Calcutta performs the extraction, as I saw it some years ago. After grinding, the seeds were defatted and then extracted and

and strychnine was isolated as nitrate.

12. Vinca species

Origin: The European species Vinca minor, Vinca major, contain the alkaloid vincamine. It was cultivated first in Hungary and the alkaloid extracted by the company Gideon Richter, Budapest.
Therapeutic use: Vincamine is used as a hypotensive and even more important as a cerebral vasodilator.
Marketing prospects: Vincamine is a product that has been gaining ground quickly in the past 5 years. The demand exceeds the production from Vinca minor. Vincamine is also obtained by the t n from Tabersonine, an alkaloid which occurs practically as the only compound in a yield of 2-3 % in the seeds of Voacanga africana and Vittouarsii. They are bushlets growing in tropical West Africa. Tabersonine can be extracted by processes of the Rauwolfia type and converted into Vincamine by a few synthetic steps.
Form of application: Vincamine is administered orally.
Technology: See under Marketing prospects. The cultivation of Vinca minor and Voacanga species seems to be strongly needed.

B. STEROIDAL DRUGS

The most important steroidal drugs are the cortison derivatives and the sex hormones, above all gestagens and estrogens, that are used in oral contraceptives. The total turn over of bulk steroids in the world is estimated to be about 475 million US dollars and the estimated usage of diosgenin for this purpose is about 350 tons of diosgenin mainly from the tubers of Dioscorea species, viz D. deltoidea (3-5 % diosgenin), D. composita (3 % diosgenin), D. floribunda (3-4 % diosgenin). However, the availability of diosgenin has become scarce on the world market due to unorganized collection of tubers from forests and also an ever increasing demand. The price of diosgenin in India has increased from 150 rupees per kilo in 1965 to 1 200 rupees per kilo in 1975. The need in India is estimated to 100 tons annually within the next 5 years. This has led to the search for new sources of diosgenin and solasodine, which is the N-analogue (in the F-ring) of diosgenin.

1. Dioscorea species

Origin: The wild-growing species that are used for extraction of diosgenin are: D. composita and D. floribunda in Mexico; D. nipponica (China), D. deltoidea and D. prazeri (India). The figures for India are the following: 400-600 tons of rhizomes are collected from D. deltoidea in the Western Himalayas and 15-20 tons of diosgenin is produced annually. A major portion of this production comes from the factory of CIMPO in Jammu and Kashmir.

Cultivated species are at present D. deltoidea and D. floribunda, both in India.

Therapeutic use: Diosgenin is the starting material for the synthesis of steroids.

Marketing prospects: Is considered to be good.

Form of application: Diosgenin is a bulk material.

Technology: D. composita and D. floribunda have been successfully grown in India in Bangal, Assam, Lucknow and many other places. The plants are climbers and are propagated from tubers cut into pieces of about 60 grams each and planted in the month of March and early April. With the advent of rains they grow vigorously and some support is provided for their climbing. The economic potential of growing D. floribunda in India is given below:

Plants per acre at 2 x 2 ft. spacing	= 10 000
Expected yield after 1 year	= 1 kg
Yield per acre per year	= 10 000 kg (fresh)
Moisture content	= 70 %
Dry tubers per acre per year	= 3 000 kg
Diosgenin (dry weight basis)	= 3 %
Therefore diosgenin per acre per year	= 90 kgs
Value at 1 000 rupees per kg	= 90 000 rupees (total retur
Cultivation costs per acre per year	= 5 000 rupees
Cost of extraction of diosgenin 300 rupees per kg	= 27 000 rupees
Therefore net profit from one acre of plantation per year, after extraction of diosgenin	= 58 000 rupees or 7 000 US dollars

Although the projected economics has been given for a 12 months crop, it will be more economical for the farmer to grow these as two year crop as then the yield becomes about 2.5 kg of tubers per plant. This crop has a high requirement of Nitrogen and potash and heavy dose of organic matter gives optimum growth of tubers. As the forests of most S.E. Asian countries are rich in organic matter, these would be ideal for large scale cultivation of these plants. Even, if instead of extraction of diosgenin the tubers are sold as such, 3 000 kg of dry tubers (3 % diosgenin) can be sold 5 rupees per kg and it will give the farmer a return of 15 000 rupees or net profit of 10 000 rupees per acre per year (= 1 200 US dollars).

2. Costus speciosus

Origin: Costus speciosus, belonging to the Zingiberaceae family, earlier not known to contain steroids, is found abundantly in the tropical rain forests in India and South East Asian countries. It has tuberous rhizomes of the appearance similar to that of ginger. The rhizomes have a maximal content of 2-3 % diosgenin at the flowering stage.
Therapeutic use: Diosgenin is the starting material for the synthesis of steroids.
Marketing prospects: Is considered to very promising.
Form of application: Diosgenin is a bulk material.
Technology: Experiments are going on at different centres to develop agro-technology for cultivation of Costus speciosus, and once a high diosgenin clone is selected, it may be more profitable to cultivate Costus as compared to Dioscorea species.
It is also propagated from tuber pieces and the advantage of this plant over Dioscoreas is that it is not a climber and yields tubers 2 to 10 kg per plant during 6 months period from the date of planting of 50 gm pieces in the month of February/March. One acre at a spacing of 2 x 2 ft. yields 10 000 tubers. The economic potential is for growing Costus in India the following:

Yield of tubers from one acre of plantation	
in one year an average of 2 kg per plant	= 20 000 kg (fresh)
At 80 % moisture content it will give	= 4 000 kg (dry)
At average 2.5 % the diosgenin yield	= 100 kg
Value	= 100 000 rupees
The cultivation costs are much less than Dioscoreas as no support for the plant is required and is estimated per acre as 2 000 rupees per year. The diosgenin extraction cost will be 30 000 rupees and the net profit will be from one year/one acre plantation	= 68 000 rupees (or 8 500 US $)

Even if the tubers are sold as such it can fetch a price of 4 rupees per kg and can give a return of 16 000 rupees per acre per year. (= 2 000 US dollars)

3. Trigonella foenum graecum

Origin: Trigonella foenum graecum has been cultivated in the Mediterrean region for many centuries for the grass (hay). Fairly recently it has been discovered that the seeds contain diosgenin.
Therapeutic use: Diosgenin is the starting material for synthesis of steroids.
Marketing prospects: According to Dr. Roland Hardman, Dept. of Pharmacy, Bath, U.K., who has worked quite a lot on this plant, the prospects should be good. I have personally only seen experimental plantations by the Pyrethrum factory in Nakuru, Kenya. As far as my knowledge goes, no large scale production is started yet.
Form of application: Diosgenin is a bulk material.
Technology: There seems to be some problems in the large scale cultivation for seeds. The large scale extraction has to be worked out on a better way than Hardman's method which is not economically feasable.

4. Agave sisalana

Origin: Agave sisalana is cultivated on a large scale for production of the sisalhemp in several tropical countries like Mexico, Kenya,

Tanzania and Madagascar. The juice of the leaves contain hecogenin.
Therapeutic use: Hecogenin is used as a starting material for synthesis of cortison-derivatives.
Marketing prospects: At present Amboni Estate Co. in Tanga, Tanzania, is preparing crude hecogenin. But it is estimated that also other sisalplantations could prepare hecogenin, since the need of starting material is so big.
Form of application: Hecogenin is a bulk material.
Technology: By preparing the sisalhemp the juice of the leaves is a waste product. But it can be pumped into big tanks, where it is airated, precipated with 0.5 % phenol and the slurry is filtrated. After filtration the precipitate is evaporated from water and dried to give crude hecogenin, which is exported to U.K. (Glaxo Ltd), where it is transformed chemically to cortisone derivatives.

5. Solanum species

Origin: Two species will be considered: Solanum laciniatum, which is cultivated on a production scale in Usbekistan, in the Chimkent region, where also solasodine is extracted. Solanum khasianum grows as a weed in India and in the plains of several South East Asian countries, as an example the Shan-State of Burma, where the fruits are collected. But since it has thorns on the leaves, the collection of berries is rather troublesome.
Therapeutic use: Solasodine (which is the N-analogue to diosgenin) is used as a starting material for the synthesis of steroids.
Marketing prospects: The Solanum laciniatum is used since a decade in Chimkent but the economy of the procedure is unknown. In India there is an optimism for cultivation of Solanum khasianum.
Form of application: Solasodine is a bulk material.
Technology: The agro-technology for S. laciniatum seems to be acceptable. The difficulty is the complete extraction of the 1-2 % solasodine in fresh plants. As regards S. khasianum the researches in India are confined to development of high solasodine containing variety with less number of thorns, which is a problem in harvesting the berries. The plants are raised from seeds, grow on wash lends, and do not require any care. One acre can yield 500 kg of dry berries, and a price of 5 rupees per kg means a

return of about 2 500 rupees (= 300 US$) per acre per year. The cost of cultivation and collection comes to about 500 rupees which means a net profit of 2 000 rupees per acre per year.

C. ESSENTIAL OILS

According to U.N. World Statistics, the trade in aromatic plants and essential oils amounted in 1969 to 282 million US dollars. As an example India shared only 1.6 %. In this context Mr. E.A. Corcoran, UNIDO Marketing Advisor, mentioned in his report 1972 that "India could grow any type of essential oil. With its diversity of soils, climates and altitudes India could grow somewhere any essential oil, which has a good prospective world market. In order to improve exports, it is necessary to diversify the variety of products seriously offered. A greater diversification of essential oils readily available in India would also be to the benefit of the Aromatic Chemicals and Perfumery Industries". In the present report only those essential oils will be mentioned, which has a medical and/or pharmaceutical application.

1. Mentha arvensis L. subspec. haplocalyx Briquet var. piperasceus Holmes

Origin: This species, which is called Japanese Mint, is suitable for large scale cultivation in several South East Asian countries. The essential oil contains about 50 % menthol.

Therapeutic use: Menthol has a broad application in medicine as well as technical use as in dental and mouth washes, cigarettes and so on.

Marketing prospects: There is a big demand for menthol on the world market and the present production is far short of its requirement. India started its cultivation 10 years ago and has now about 10 000 acres of cultivation, yielding about 200 tons of essential oil and 100 tons of menthol to a value of about 30 million rupees annually.

Form of application: Menthol is used orally and topically in many forms.

Technology: It grows well in fertile, sandy loam, well drained soils, in open areas having annual temperature varying from 2 to

35°C and annual rainfall of about 40 to 50 inches or more. It is propagated from rootstock cuttings in the month of February/March. The first harvest is ready after 4 months when the plants are in flowers and the second harvest is ready after 4 months again. Third and subsequent harvests can be taken after similar 4 months period, but it is economical to take it out after 2 harvests and then to rotate it with other crops as wheat, potato etc. After harvesting, the crop is allowed to wilt by drying in the shade and then cut into pieces and poked in the still for extracting the oil by steam distillation. Menthol crystals are obtained by chilling the oil and recovery is about 60 %.

An acre of herb yields annually about 40 kg of oil valued in India to 4 000 rupees and if the menthol is extracted, the return becomes 6 000 rupees. The cultivation costs come to about 1 000 rupees per acre per year and distillation costs about 10 rupees per kg of oil. A small distillation unit to serve 5 acres of plantation costs about 5 000 rupees (600 US dollars) but in large plantations boiler with bigger distillations units are used.

2. Mentha piperita

Origin: This species which has many varieties, is the peppermint, which is cultivated on large scale in Japan, USA and Brasil, has also been introduced to India and Thailand for peppermint oil and menthol production.

3. Cymbopogon flexuosus

Origin: There are varieties of this plant with different citral content. Up to now the best variety is SD 68, which has 90-92 % citral content in the essential oil, called Lemongrass oil.
Therapeutic use: Citral is converted into β-ionone, which is the starting material for the synthesis of Vitamin A.
Marketing prospects: There is great demand for lemongrass oil, and India exports about 20 million rupees of this oil annually. If it is produced in South East Asian countries, it is considered to be a very good source of revenue.

Form of application: Lemongrass oil is a bulk material.
Technology: The plants are propagated from rooted slips for preserving the strain. These are set in the field during rainy season at a distance of 90 cm between rows and plants. Normally it takes about 2 weeks for the slips to establish and put on new growth of leaves. In about 16 weeks the grass attains a height of about 5 feet. The plants propagate very rapidly and from one plant about 50 slips are obtained in the course of one year. The first harvest is obtained after 6 months and thereafter at an interval of every two months. Foliar manure in the form of 1 % urea spray is given after each cutting and NPK fertilisers are also given to the ground.

The oil yield has been upto 100 kg per acre and in India the price is 60 rupees per kg. It can give a return of 6 000 rupees per acre per year. (US dollars 750)

D. LEUCODERMA DRUGS

1. Ammi majus

Origin: The fruits of this Umbelliferous plant contain xanthotoxin.
Therapeutic use: Xanthotoxin is used in the treatment of leucoderma.
Marketing prospects: Is considered to be acceptable.
Form of application: Xanthotoxin is administered locally.
Technology: The plant is easy to cultivate and can be produced from the fruits. It is a short term crop planted during winter months in the plains and can be cultivated in almost all South East Asian countries. One acre produces about 400 kilos of fruits, and in India the price is 6 rupees per kilo. This can give a return of 2 400 (= 300 US$) per acre per year, whereas the cultivation and collection costs come to 600 rupees per acre per year.

2. Heracleum candicans Wall

This plant is a new promising source of xanthotoxin, but further details about technology are not available.

3. Psoralia corylifolia L.

This plant contains psoralen, which also is used in the treatment of leucoderma. If the present clinical trials for using psoralen in psoriasis therapy will be definitely positive, this plant will be of great importance.

E. INSECTISIDES

1. Chrysanthemum cinerariaefolium

Origin: The crude drug Pyrethrum consists of dried flowers of the plant Chrysanthemum cinerariefolium, the main country of production being Kenya with the factory in Nakoro (which I have visited). Other species, viz. C. coccineum and C. marschalii are also considered as sources of Pyrethrum flowers and these are found in Yugoslavia, Iran and Japan.
Therapeutic use: Pyrethrum is a very important insectiside with a mixture of active compounds: pyrethrins and cineranins.
Marketing prospects: After the ban of DDT, the market of pyrethrum has increased enormously, and the present production is not enough.
Form of application: Mainly as powder and as extract for spray of different types.
Technology: The three species grow best in warm localities and in ordinarily manured or fertilized field or garden soil which is well drained and not too clayey. It is propagated from seeds or by divisions of the old plants. The seeds are mixed with sand and sown broadcast on the surface of seedbed and covered thinly with with soil. They are sparingly watered and they germinate in about two weeks. In from 4 to 5 weeks after germination the seedling should be transplanted to the field and set 9 to 12 inches apart in rows about 3 feet apart. Weeding from time to time is necessary as it gives better yield of flowers. The flowers are collected when the ray florets are just opening as at this time pyrethrin content is maximum, and dried in the shade or sun.

C. cinerariaefolium has been grown in India at high altitudes about 5 000 to 6 000 ft or more and it does not require rich soil. It has

been grown commercially in Kashmir in India and the yield per acre is about 300 kg over a period of 8 months. At a price of 12 rupees per kg, the average return per acre per year is 3 600 rupees (450 US dollars). Its cultivation in some of the S.E. Asian countries is worth trying as there is great demand for it as the best insecticide, harmless to mammals and human beings.
A programme to produce 300 tons of Pyrethrum flowers in India (present production is 50 tons) during the next three years has been chalked out as a new Regional Centre of CIMPO is opened exclusively for this purpose in South India (in Tamilnadu state).

2. Derris elliptica

Origin: The root of Derris elliptica, D. malaccensis and other Derris-species contains rotenon.
Therapeutic use: Rotenon is a very important insectiside and fish poison.
Marketing prospects: Is considered to be very good. There has been a shortage of rotenon-containing drugs for the last two decades.
Form of application: Powdered root or extract in sprays of different types.
Technology: The detailed informations on cultivation and economy is not available at present.

F. HYPOCHOLESTEROLEMIC AGENTS

Since clofibrate which is practically the only drug used in the Western world for the treatment of hypercholesterolemia and hyperlipidemia, has so strong side-effects, it has been forbidden in several countries. Therefore there is certainly a big need for such a drug, especially a natural product. Two drugs will be considered here.

1. Commiphora mukul

Origin: This plant, belonging to the family Burseraceae, grows abundantly in Rajasthan and Gujrat and is also available in Mysore, Deccan, Khandesh, Kathiawar and Rajputana desert.
An oleo-resin is secreted by this plant, specially in summer, which

is commonly known as "Guggulu".
Therapeutic use: It is reputed in the Ayurvedic system for different ailments, particulary for its anti-arthritic activity and also for the treatment of "Medo-Roga" (lipid disorders including obesity). The oleo-resin was observed to possess marked hypo-cholesterolemic activity. It has been found that the ethyl acetate extract (named Gugulipid) of the resin, which accounts for about 40 % of the total resin, causes a marked lowering of the serum lipids.
Marketing prospects: If the clinical trials continue to be as positive as up til now, the market is enormous, and will be an excellent product for export.
Form of application: The oleo-resin is given 10-15 g orally, the ethyl acetate extract (Gugulipid) in half the dose.
Technology: At present it is wild-growing, but it is forseen that a cultivation would be motivated in the near future. The agro-technology of this plant as well as the best way of collecting the oleo-resin should be worked out.

2. Anethum graveolans

Origin: This plant is known as the spice "Dill", and it occurs in different forms and chemotypes. Especially the chemical differences in essential oil from different "Dill" is investigated. However, the discovery of the hypolipemic action of "Dill" is made in Afganistan and at present it applies to the "Dill" grown here.
Therapeutic use: As a hypolipemic agent. The active principle and its mechanism of action have yet to be elucidated.
Marketing prospects: If further clinical trials are positive the market is enormous, and it will be an excellent product for export.
Form of application: Up to the present the fresh and/or the dried herb has been used. However, when the active principle is found a suitable extract should be made and administered in gelatin capsules.
Technology: The cultivation of dill is wellknown. The problem to be solved is the extraction of the active principle on an industrial scale.

G. EXPECTORANT DRUGS

1. Glycyrrhiza glabra

Origin: The root of this plant is the liquorice.
Therapeutic use: The extract has technical use (to produce foam for fire extinguishers, for mellowing tobacco, in the confectionary and liquor industries) and pharmaceutical use as expectorans in cough siroups. Pure substances: 1) Glycyrrhizic acid in the form of the monoammonium or monopotassium salts is used as a nontoxic sweetener and taste corrective. 2) Glycyrrhetic acid as succenyl derivative or aluminium salt is used the treatment of some forms of ulcer. The annual consumption of these two products amounts into tens of tons.
Marketing prospects: A variety with a high content of glycyrrhizic acid has enormous possibilities at present and in the future.
Form of application: The extracts are administered orally in the cough siroups, the pure substances orally or otherwise.
Technology: The preparation of glycyrrhizic and glycyrrhetic acids involves numerous processes. The ground liquorice roots are extracted with boiling water and the extracts are highly concentrated or purified with resins, according to the type of equipment, and treated with acids to render the crude glycyrrhizic acid insoluble. This crude glycyrrhizic acid, treated with ammonia or with the base whose salt one wishes to obtain, through crystallisation from acetic acid, and, through successive crystallisations from dilute alcohols, supplies the monoammonium or monopotassium glycyrrhizinates, which are the utilisable products. Although three carboxyl-groups are present, crystallisation always supplies a monobasic salt and so in the first crystallisation one can operate with an excess of cations. For the preparation of Glycyrrhetic acid too, there are a number of processes ranging from direct sulfuric hydrolysis of the drug to acetylating hydrolysis of the crude glycyrrhizic acid conducted in acetic acid and sulfuric acid. Glycyrrhetic acid can be obtained industrially either by acetylating hydrolysis of the crude glycyrrhizic acid, purification of the acetyl derivative and saponification or by acid hydrolysis, extraction of the terpene fraction with chlorinated solvents and acetylation of the residue. Because of its high degree of

insolubility in the most common solvents, acetylglycyrrhetic acid is easily purified. Alkaline hydrolysis gives excellent yields of glycyrrhetic acid.

H. ANTIPARKINSONISM DRUGS

1. Mucuna pruriens

Origin: The seeds of this plant contain L-dopa.
Therapeutic use: L-dopa is one of the imported drugs in the treatment of parkinsonism.
Marketing prospects: Since this plant only contains the active L-form, it can compete with the synthesis, where the racem-form obtained has to be resoluted.
Form of application: Orally as tablets.
Technology: Technical details not available. A good method of extraction and purification is essential.

I. CARDIAC GLYCOSIDES

The dominant drug is Digitalis, and the species Digitalis lanata is the most widely cultivated plant. The squill, the bulbs of Urginea maritima and g-and k-strophanthin from the seeds Strophanthus gratus and S. Kanbé, are still in common use in the Western world. However, owing to further investigations and availability of new drugs two new drugs will be mentioned, one of which is in clinical practise in Europe, whereas the other, asclepin (from Asclepias curassavica), is in experimental stage and requires clinical trials.

1. Thevetia neriifolia

Origin: This small tree or bush originates from Peru, but is now pantropical, mostly used as ornamental tree owing to the nice yellow flowers. The fruit contains peruvoside as the primary glucoside.
Therapeutic use: Cardiac glycoside with moderate accumulation.
Marketing prospects: This glycoside has become quite a success in

Central Europe and will certainly have a bigger market in the future.

Form of application: Orally in tablets or i.v. - injection.

Technology: The primary glycoside is converted into peruvoside by water treatment of the ground drug at its natural pH at a temperature of 50-60°C. Fermentation occurs very quickly; the active principle is extracted with an alcoholic solvent, the percolates are defatted by extraction with non-polar solvents of the petroleum eter type and then extracted with methylene chloride. After chromatography on silica gel, pure peruvoside is obtained by chrystallisation.

J. SEDATIVES

The need of a good mild sedative is very big. There is at present only the Valeriana-root in this cathegory and an intensive research is here strongly recommended to find a new drug.

1. Valeriana wallichii

Origin: This is an Indian species, which has a higher content of the active principle, valepotriate, than the European species, V. officinalis.

Therapeutic use: Mild sedative.

Marketing prospects: Is considered to be good, also for export.

Form of application: Orally in tablets or drugs.

Technology: Detailed informations are not available at present.

K. SAPONINS

1. Aesculus hippocastanum

Origin: This species is the well-known horse chestnut, which is cultivated as an ornamental plant in temperate zones.

Therapeutic use: Three products are in current therapeutic use: 1) escin (the major constituent), 2) the purified extract, 3) esculoside. The most extensively used compound today in Europe is escin, a very complex but well characterized mixture of

saponins, that may be considered as a pure product.
Marketing prospects: Good and is considered to be even better.
Form of application: Orally and parenterally.
Technology: It is important to note that the acids in positions 20-21 give rise to acylic migration as a result of prolonged heating or in the presence of acids. The isomerised products seem to lose nearly all their activity; certainly the hemolytic index falls from 40 000 to 20 000. This point must be kept in mind in the industrial preparation of the compound. There are numerous patents for producing Escin or saponins from Horse-chestnut. There are fundamentally two processes. One is based on the saponin-binding power of cholesterol or phytosterols and the other on the separation of saponins in the form of free acid by crystallisation In the cholesterol process the drug is extracted with alcohols and the percolates are highly concentrated and treated with cholesterol either in solid form or in ethereal solution. A cholesterol/escin complex is formed and this, like the one formed by digitonin and cholesterol, is practically insoluble and quantitative: the centrifuged complex is treated with solvents that dissolve cholesterol only, such as chloroform, toluene and the like. The cholesterol free saponin can be either crystallised from alcohols - in which case escin is obtained in the form of the natural salt, a mixture of sodium and potassium - or treated with acids or cation resins and crystallised in the form of the free acid.

The other process involves extraction of the drug with isopropanol, treatment of the final concentrate with a cation resin and crystallisation of escin as a free acid. It is worth saying a few words on the crystalline form of escin, which is the most commonly used form of the saponin. Escin as the free acid is sparingly soluble in water, especially in the cristalline form. Administered orally, this product is thought to be poorly adsorbed whereas in the amorphous form adsorption would be better. There is a patent for a special type of micronisation that renders the compound completely amorphous on X-ray analysis. In this form adsorption of the compound and hence its activity are definitely increased.

L. LAXATIVES

1. Plantago ovata

Origin: This plant, belonging to the Middle East flora, was introduced to India during Moghul rule and was given the name Ispaghula. The seeds and husk are used, called Psyllium seeds or Ispaghula seeds. India is one of the major producers of this drug, bulk of which is exported.
Therapeutic use: Standard bulk laxative throughout the world.
Marketing prospects: The production of this drug in India is confirmed to some areas in Gujrat and Rajasthan and at present about 16 000 hectars are under cultivation with an annual production of 12 000 tons of seeds and husk. There is a big demand on the world market, and further cultivation is motivated.
Form of application: Ispaghula is administered orally in various forms.
Technology: The cultivation of this plant could be undertaken in drier areas and it is a short term crop of about 4 months. It is propagated from seeds and prefers somewhat sandy soils. The yield is about 700 kg per hectar.

2. Cassia acutifolia and cassia angustifolia

Origin: These two plants produce senna leaves and senna pods, C. acutifolia is mainly cultivated in Sudan and C. angustifolia in South India in Tinnevelly district.
Therapeutic use: The anthraquinone glycosides in leaves and pods have a laxative effect, acting on the muscles of colon to produce peristalsis. Now mainly a standardized product of sennosid A + B is used.
Marketing prospects: India is one of the major exporters of senna leaves. At present approximately 1 800 hectars of land are under cultivation producing approximately 2 500 tons of leaves and 800 tons of pods. Indigenous technology for processing the leaves have been developed and attempts are being made to promote export of finished product, namely the sennoside A + B mixture.
Form of application: Orally in tablets.

Technology: The plant is propagated by seed which is planted in nursery beds usually in December. The young plants are transplanted in February when about 6 cm in height and are spaced 1 x 1 m. Profuse watering is needed during the months of April and May but shading is not required. The plant is stripped three times during the season, the first picking starts in May. Immediately after picking, the leaves are dried in the sun and quick drying ensures an excellent colour. It could be easily grown in S.E. Asian countries as the climatic and soil factors there are mostly similar to S. India, where the yield is about 600 kg of leaves per acre per year valued 3 000 rupees (= 375 US dollars).

III CONCLUSIONS AND RECOMMENDATIONS

Three types of natural products have been dealt with in the previous chapter; i.e. crude drugs, purified extracts and isolated pure compounds. There is a good demand in the world trade for all three categories of commodities. This applies for the treatment of communicable, infections, tropical and other relevant diseases.

An increased production of the three aforementioned items involves two steps: Firstly, an increased large scale production of established medicinal plants now in current use and the introduction of new medicinal plants and their large scale cultivation. Secondly: the development of an indigenous industry in the developing countries for extraction of the crude drugs to produce purified extracts and/or pure compounds.

For the implementation of the aforementioned goal the following practical achievements are strongly recommended:
1. Setting up of an Advisory Board under UNIDO with a maximum of five experts in a) Tropical agriculture, b) Pharmacognosy including Phytochemistry, c) Pharmacology, d) Marketing, e) Pilot plant and industrial extraction processes.
This advisory board shall evaluate the prospects of increasing production of crude drugs, firstly in South East Asian countries, secondly in African and American countries. The advisory board

shall also give the guidelines and draw the Master Plan for the research and development in this field.

2. Establishment of a South East Asian Institute for Research and Development of Medicinal Plants: In fact, such an Institute was planned by UNESCO in 1961, later built by the Goverment of Pakistan, and now belongs to Bangladesh Council of Scientific and Industrial Research. It is situated in the outskirts of Chittagong, between the city and the university. It is a hugh building to which is attached a big fenced area for experimental cultivation of medicinal plants. Animal house and pilot plant factory is also available. But unfortunately the equipment is poor and a meaningful scientific activity is almost non-existing. At my visit there in the end of February 1977, I got the impression that the manpower was mainly used for arrangements in the experimental plot and plantation in the Chittagong Hill Tracts. I had a serious discussion with the director, professor Khan, who was aware of the shortcomings but was very positive to transform the present institute into an International (=South East Asian) entity.

This is also my realistic proposal: The building, land and partly staff is already available; what is needed is a meaningful scientific activity in this field. It needs inspiration, new ideas and initiatives. I will strongly recommend UNIDO to take the necessary steps in this direction by negotiating with the governments that will be involved in the running costs. The activity should start with simple, practical problems, not sofisticated basic research. As an example: To find the best cultivation conditions for senna and work out the method for the determination of the sennoside A + B content. Another urgent practical problem is the cultivation of Valeriana Wallichii and determination of its valepotriate content under various conditions.

It is foreseen that there will be a participation of scientists of various types from the contributing countries in the research and development activities. The results should, of course, be available for those countries free of charge.

Seen in a longer perspective, the activities of the institute should include the following programme, which has to be developed gradually, step by step, as the manpower and equipment will be available:

1) Studies on sowing and germination for finding out optimum conditions.
2) Studies on the behaviour, morphological variations and ecological adaptations of the plants from seedling to harvesting stage.
3) Studies on ecological factors influencing growth under different climatic conditions at different elevations.
4) Studies on soil conditions of different places where the plants are grown with a view to correlate the difference in growth patterns and variation in active principle content.
5) Studies on collection, curing, drying storage and extraction techniques in pilot plant and industrial scale.
6) Studies on the improvements of plants by cytogenetical and selection methods with a view to produce improved varieties and strains.
7) Studies on plant pathological problems for controlling diseases of plants.
8) Studies on the effect of organic and inorganic manure in the variation of active principle content.
9) Effect of trace elements on growth and active principle content of these plants.
10) Effect of irradiation for producing better varieties.

3. The problem of utilisation and application of the results of the research and development projects of the institute for the participating countries will create only minor problems. Probably it is most efficient to create in each country a National Drugs Promoting Board, which will have the necessary contacts with the Forest and Agricultural Departments and private firms and companies, i.e. those bodies that shall carry out the large scale cultivation and extractions. It is quite obvious that the various Drugs Promoting Boards shall have regular contacts and discussions with the Advisory Board. There should be reciproke exchange of ideas, proposals and initiatives.

The aforementioned Research and Development Institute should be regional in character, for 8-9 states in South-East Asia.
4. Remains Africa and America! It is my firm belief, based on 20 years of experience of developing countries, that there must be such a regional research and development institute both in America and Africa.

My present trip to Africa was meant to give a supplementary background to my previous trips to tropical Africa. The basic idea was similar to that for Asia: An existing institute is proposed to be transformed into a regional, in this case a Pan-African Institute for Research and Development of Medicinal Plants. The reason for including Gabon in this trip, is the fact that the laboratory for primatology and ecology, run by the French organization C.N.R.S., in Makokou, is now in a state of nationalisation or "gabonisation" with probably other or wider field of research. During my stay there a five-men-delegation of gabonese officials visited the place 8-11 November 1977. Important for the idea of transforming this laboratory to a Pan-African Medicinal Plants Institute was that Dr. Jean-Noel Gassita, Directeur de l'Institute de Pharmacopée et de Medicine Traditionelle, Libreville, was present and we had several discussions. Although the research station is very nicely situated on the banks of the Ivindo River, the laboratory space is very limited and equipment is non-existing. From the present hobby activity it is easy to get monkeys for animal experiments, but there is no suitable land nearby for experimental cultivation. Much to my regret it must be stated,- according to my sincere judgement,- the Makokou station is no ideal solution. - It will be an expensive but beautiful solution.
But there is another institute, namely the O.R.S.T.O.M.-Institute in Adiopodoumé, 17 km outside Abidjan, that could be the ideal place for the future Pan-African Institute for Research and Development of Medicinal Plants. I have worked there twice, when collecting plant material for phytochemical investigations and I was impressed by the many good facilities and useful equipment. I only regret the rather meager research activities. To the facilities can be included considerable land for experimental cultivation of medicinal plants. One advantage is that already now

tropical agriculture is represented. A pilot plant is missing, which is the only draw-back, as far as I can see. In fact there are so many advantages (all not mentioned here) with that research station, that I will strongly recommend UNIDO to take up the negotiations with the government of Ivory Coast and ORSTOM for realisation of this project.

Owing to climatic conditions the projects to be dealt with will be restricted to tropical Africa, i.e. the countries south of Sahara.

Its organization and future research activities should be similar to that of the South East Asian Institute, a coordination of the activities being recommended.

As regards America I have unfortunately no constructive proposal at present.

IV APPENDIX 1; Production of crude drugs by Dr. S.C. Datta

Production of crude drugs on commercial scale and for profit involves a number of factors. The value of a medicinal plant depend on its active principle content and not on its luxurious growth which makes it different from the principle of production of agricultural crops. It is often found that the same plant grown in different localities differ widely in their medicinal value and for this reason the medicinal plants collected from different regions and sold in the market are found to differ in quality. Several factors as soil, storage, marketing etc. play an important part in the production of crude drugs and some general informations on these points are given below.

1) Soil - Soil, as understood by growers of plants it is the part of earths surface usually 10 to 45 cm deep and is formed as a result of the weathering of the underline rocks by wind and rain and breaking down of particles by expansion and contra action due to climatic conditions and decay of vegetable matter and the action of earth worms. The following types of soil viz., clay, sand, gravel, chalk, limestone, peat, granites and loam are usually met with and the soil type is often an important limiting factor in propagating different kinds of plants as some plants grow best in well-drained loam, some require acid soil, whereas others like alkaline soil or prefer marsh. In undertaking the growing of medicinal plants, therefore it is essential to know that the species selected for cultivation will do well under the conditions of soil which the plant prefers. Soil sterilisation may also sometimes be necessary for ridding insect and other pests and for this, baking, steaming, scalding or fumigation by spraying of chemicals is done, the common fumigant being napthalene and lime in equal quantities. Other fumigating materials available in the market are also used.

2) Climate - Next to soil the most important factor is the climate. Tropical plants would not grow in the temperate region, nor mountainou plants at the sea level although there are exceptions. Many plants also grow successfully if exposed to more light while a number of

others prefer a shady atmosphere. Such factors are of importance in the growing of medicinal plants.

3) Propagation - Plants can be propagated either from seeds or by cutting, grafting and layering. The preparation of the soil is of importance in raising the plants from seeds. Very small seeds do not germinate in heavy soils and a seed bed prepared by mixing equal parts of garden soil, leaf mold, well rotted manure and clean sand proves good for germination of most seeds. The depth of sowing is also an important factor and smaller seeds need shallow sowing. In case of open sowing in the field seed drills provide more uniform and good germination.

Propagation by cutting is also important for keeping the plant true to type. The general rule is to cut immediately below a leaf joint, because roots develop easily at this point. Use of hormones and Seradix for profuse rootings give quick and better results. In case of budding and grafting, a bud or an eye or short terminal stem from the special variety to be propagated is transferred to a well established plant of some common kond. The result is that the new shoot receives the support of an established plant and grows with increased vigour. Propagation by layering is another process where the plant is encouraged to form root before being detached from the parent.

4) Cultivation - There are no set rules for the cultivation of medicinal plants and the experience of the planter with a particular plant is to be relied upon. As a general rule, the soil should be worked with the hoe or cultivator at frequent intervals and kept free of weeds. It is a good practice to prepare the soil after a hard rain when the ground is sufficiently dry. Application of fertilisers and manures in requisite quantities is also an important factor in cultivation. Nitrogen in the form of urea or ammonium sulphate, potassium salt and super phosphate are the three most common fertilizers. Nitrogenous manures increase vegetative growth and produce dark green foliage, potash increases quality and assists resistance to disease and phosphorus provide fruitfulness and early ripening. Calcium, Magnesium, Iron salts and trace elements as Zinc, Boron etc. also have effect on development of

plants. The plant diseases are also important factors to be considered during cultivation. They are caused by insects, fungi, bacteria, viruses or deficiency of plant nutrients. The best method for getting disease free plants are prevention, which consists in keeping all plants clean, burning all diseased leaves or twigs, cutting down weeds which are disease carriers and maintaining a proper balance of fertilisers in the soil. For preventing fungus attacks the following fungicides are of common use (1) Sulphur, (2) Potassium permanganate diluted to a pale brandy colour in water, (3) Bordeaux mixture, i.e. sulphate of copper 1 lb.; lime (freshly burnt) inlumps 1 lb; water 12 gallons. The sulphate and the lime are dissolved in separate vessels and the sulphate solution poured into the milk of lime and stirred thoroughly. This mixture is strained and then applied as spray. There are several other fungicides available in the market. Insects also do considerable harm to crops and the following insecticides are of common use: (1) Carbolic acid, 1 pint, soft soap 1 lb., water 10 gallons; (2) Caustic soda 3 lb and water 10 gallons; (3) Lead arsenate; (4) Lime sulphur, (5) Nicotine 3/4 ounce, soft soap 1 lb and water 10 gallons, (6) Paraffin emulsion consisting of paraffin 1 pint, soap 1 lb and water 1 gallon and (7) Copper sulphate 1 lb dissolved in 10 gallons of water. Besides the above many systematic and other kinds of insecticides are available in the market. Another method of control is to introduce competitive insects, fungi and bacteria that are harmless to plants but are detrimental to the affecting organisms.

5) Collection and harvesting - The time and season of collection is an important factor in medicinal plants, as the active principle content varies due to age of plant, time of flowering and fruiting, seasonal effect, periodic changes due to alternation of day and night, locality and altitude. The following rules for collection of drugs are in practice:

a) Roots, rhizomes and barks are collected in late autumn or early spring when the vegetative processes have ceased.

b) Leaves or flowering tops are collected about the time of development of flowers and before the maturing of the fruit and seed. At this time the photosynthetic activity is at its maximum and the content of the active principle is also high.

c) Flowers are collected prior to or just about the time of pollination.
d) Fruits are collected when full grown but unripe.
e) Seeds are collected when fully mature and if possible, before the fruits have opened.

6) Drying - The appearance of crude drugs and their quality are often dependent on their mode of drying. The object of drying is to remove sufficient moisture from the drug so that it may develop keeping qualities and help in prevention of fungal attacks and control of chemical and enzymatic changes. Medicinal plants, after collection are dried either in the sun or shade or by artificial heat in commercial driers with arrangement for control of temperature and regulation of flow of air. The latter method is most preferable. The temperature requirements for drying certain drugs like Belladonna, Digitalis etc. are specified in the Pharmacopoiea as they have effect on the active principle content.

7) Storage - Proper storage and preservation methods are essential for maintaining a high degree of quality of the drug. The storehouses should be rodent-proof, cool, dark and well ventilated with dry air. Drugs, not well packed, absorb moisture and this favours enzymatic activity and fungal growth leading to spoilage. To prevent insect attack, fumigation with methyl bromide or exposing the drugs to a temperature of 65^{o}C gives good result. Preservation in tinned cans or metal containers is preferable to paper package. If the container is air-tight, the insect attack can be prevented by addition of a few drops of chloroform or carbon tetrachloride. In cases of drugs like Digitalis, which deteriorate in the presence of moisture, the insertion of a suitable dehydrating substance in the container, without allowing it to come in contact with the drug is considered useful. The ideal temperature for preservation of drugs is just above freezing point but if this is not available the temperature should be maintained as low as possible.

8) Marketing and commercial prospects - The crude drugs after collection should be marketed as soon as possible and it will be

advantageous to get in touch with pharmaceutical concerns, which use them beforehand. Samples may also be sent to drug dealers to find out other channels of selling. It will be advantageous if the producer can furnish data on chemical constituents of the drug, in order to assure the purchaser that the material is of standard quality. Data on pharmacognostic characters which are mentioned in the pharmacopeia will be useful for determining genuineness and detecting adultration.

Although some of the medicinal plants show high prospects of return, quick returns and making large profits is not easy. This is because their production requires specialized knowledge as explained above, and every stage of production has to be pursued scientifically with proper care and attention. Moreover, knowledge regarding production of medicinal plants as compared to well-known agricultural crops is not widespread and during the first two or three years, some experimentation will be necessary to find out the optimum conditions favourable to a plant with respect to the particular locality in which it is grown. Introduction of improved varieties of plant is also an important factor and this will definitely bring more profit than the ordinary variety. Seeds or planting materials of such improved strains are available with Government Agricultural, Forestry or scientific organizations and in India, Indian Council of Agricultural Research, New Delhi, Central Indian Medicinal Plants Organization, Lucknow and Forest Research Inst., Dehra Dun are in a position to supply the same. Some of the medicinal plants can also be grown as side crops and small scale cultivations can derive an additional income from such production. However, inspite of the above difficulties, the crude drug industry has a very bright future and recently several new crude drugs have come into prominence and their demand is also very high in the market. Production of such new items are possible in the South East Asian countries as the climatic and edaphic factors are suitable for their production and details about them are given in this paper.

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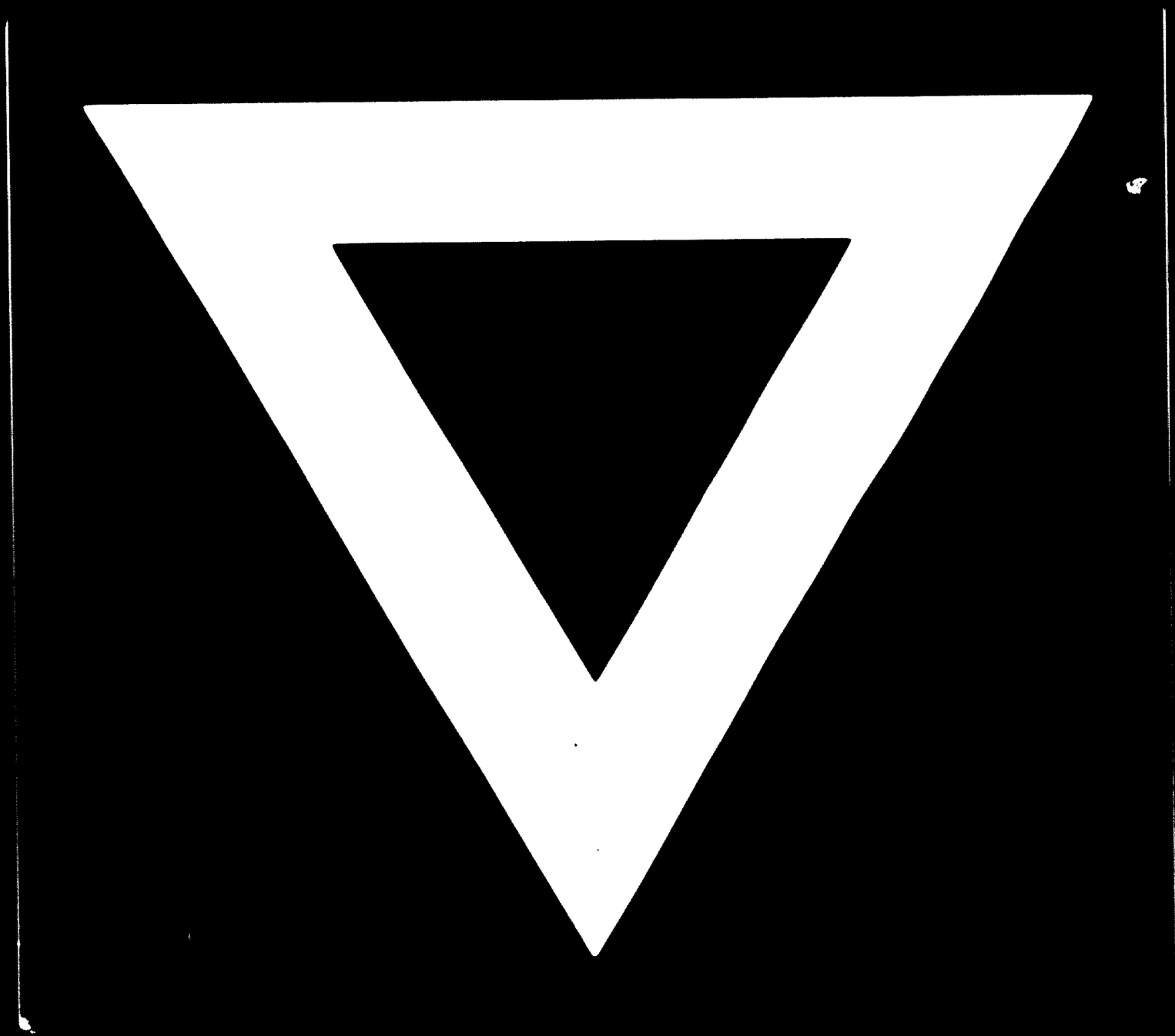

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