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Herbal Medicine For Human Health

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The sketch of **Artemisia annua**, *appearing on the cover, is reproduced from the issue of* **'World Health'**, *September-October 1991.*

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FOREWORD

THE human race, over the centuries, has developed a wide variety of technologies with due regard to nature and the ecosystem. Exploration of medicinal properties of plants, extracts of animal and marine life had created, through careful observation, trial and error, a vast heritage of knowledge and expertise in different cultures and civilizations. Most of such indigenous knowledge was handed down, through the ages, by oral tradition. In particular, in Asia, well-established systems of medicine were in vogue even before modern medicine made its debut.

Modern science is founded on the belief that knowledge, as it progresses, accumulated new and improved concepts driving out the old and the fallible. It prides itself on being objective and rigorous; yet it fails to recognize that there can be other systems of thought. Phytotherapy, or herbal medicine, believes in the harmonious view that "the whole plant is greater than the sum of its parts". Some of the wonder drugs of modern medicine have their roots in indigenous medicine.

We have yet to explore fully the vast storehouse of indigenous, tribal or folklore and traditional systems of medicine. We have to recognize that wisdom has its value. Luckily, there is a realization today that there is a need to preserve the enormous trove of wisdom and traditional knowledge as also the cultures associated with them. Not only must flora and fauna be protected but also the knowledge data base often stored in the memories of elders and traditional healers.

In this excellent volume, Professor Chaudhury, with his deep interest in health care and profound experience in pharmacology, has dealt with a broad spectrum of related issues in a meticulous manner. I am very pleased with this timely effort and sincerely hope that scientists in Asia will establish a data base of herbal medicine and use the newly emerging computer modelling techniques to expand on our inherited wisdom.

Dr U Ko Ko
Regional Director

ACKNOWLEDGEMENT

THIS book would not have been written without the generous support and help received from many different persons during my stay at Oxford in the summer of 1990. I am grateful to Professor Sir E.P. Abraham for his continued encouragement, advice and help throughout our long association. I would like to thank Professor A. David Smith for giving me again a home at the University Department of Pharmacology after thirty-two years and for making available to me all the facilities at the Department during my stay at Oxford.

The Governing Body of Lincoln College, my college, very kindly elected me a member of the Senior Common Room, which privilege I greatly valued and appreciated. I would like to thank Sir Maurice Shock, Rector of Lincoln, and the Fellows for this very kind gesture, which added a different dimension to my stay at Oxford. I am grateful to Dr U Ko Ko, Regional Director for South-East Asia, World Health Organization, New Delhi, for giving me leave of absence from Myanmar where I was serving as WHO Representative, to go to Oxford to write the book. I would also like to acknowledge the suggestions and helpful comments on the different topics included in the book received from my former teachers and colleagues at the Department of Pharmacology: Dr J.M. Walker, Dr E. Gill, Dr H. Blascho and Professor Sir W.D.M. Paton. A new avenue of thought was opened up for me after my discussions with Professor F.R. Whatley of the University Department of Botany.

The section on Regulation would not have been possible had I not received help from the different departments of different governments. I would like to thank the following for collecting and sending me background

material regarding existing regulations in different countries: Dr S.L. Nightingale (USA), Dr J.E. Aldred (Australia), Dr R.A. Armstrong (Canada), Dr G. Satyavati (India) and Dr Wang Zhen Ghang (People's Republic of China).

I acknowledge with thanks the permission received from the Regional Director for South-East Asia, WHO, to refer to the proceedings of the WHO Interregional Workshop on the Selection and Use of Traditional Remedies in Primary Health Care, held in Bangkok in 1985.

I acknowledge with thanks the permission received from the Regional Director for the Eastern Mediterranean, WHO, Alexandria, to refer to the following:

- *Proceedings of the Intercountry Meeting on Use of Medicinal Plants at the Primary Health Care Level, Kuwait, in 1985.*
- *Act aimed at ensuring the safety and quality of herbal remedies (The Herbal Remedies Act) and Notes for Guidance, Alexandria 1985.*
- *EMRO Document WHO-EM/Pharm/105/Alexandria 1985 on draft guidelines on requirements for regulation of drugs.*

I recall with great pleasure the years 1982-1986 spent at this Regional Office when I was associated with the programme of essential drugs and traditional medicines under the leadership of Dr A.R. El. Gezairy, Regional Director. I received valuable help and many suggestions from my colleagues at this time which gave me the idea for this book.

I acknowledge with thanks the permission received from the Regional Director for the Western Pacific, WHO, Manila, to refer to the following:

- *Proceedings of an Interregional Seminar on The Role of Traditional Medicine in Primary Health Care, People's Republic of China, 1985.*
- *Proceedings of an Interregional Meeting on Standardization and Use of Medicinal Plants, Tianjin, People's Republic of China, 1986.*

I am very grateful to the Trustees of the Edward Penley Abraham Research Fund and the EPA Cepholsporin Fund for their help which enabled me to spend this very pleasant and useful time in Oxford.

It was a pleasure to have used the following libraries during my stay in the United Kingdom and to have received help from the persons in charge: Radcliffe Science Library, Oxford; Wellcome Unit for History of Medicine, Oxford; Social Anthropology Department Library, Oxford; and the library of the International Planned Parenthood Federation (IPPF), London. During my last visit to the library in London, I was fortunate to have a most stimulating and thought-provoking discussion with the Secretary-General, IPPF, Dr H. Mahler, former Director-General of WHO.

I acknowledge with thanks the help received from Mrs G. De Visscher then Acting Regional Adviser, and from Mr S.K. Anand, Regional Librarian in the WHO Regional Office, in collecting relevant material, and from Mr N.A. Doraiswami, who assisted with the editing of this publication. I am grateful to Dr Palita Abeykoon, also of the Regional Office, for his encouragement and advice.

This book was completed at the National Institute of Immunology. I acknowledge with appreciation the facilities and help provided to me by Professor G.P. Talwar, Director of the Institute.

Finally, I am grateful to Sir E.T. Williams, former Secretary of the Rhodes Trust, for his constant interest in my work over the many years since I went to Oxford as a Rhodes Scholar in 1955, and to Lady Gillian Williams, specially for arranging a visit to the Chelsea Physic Garden in London.

Dr Ranjit Roy Chaudhury

Chapter 1
WHY HERBAL MEDICINES?

MILLIONS of people in the third world will always use herbal medicines because they believe in them. They also regard them as "their" system of medicine. It is a system in which they have faith. They deal also with practitioners whom they have always known and with whom they are comfortable. This was brought home strikingly to the author while visiting a traditional medicine clinic in rural Myanmar (Burma). In answer to his question as to why an elderly patient visited that clinic instead of the allopathic hospital next door, she said simply: "Because this is our system of medicine". On further questioning, she just added: "I believe in the value of the medicines".

Factors such as easy availability of herbal remedies, accessibility to practitioners at all times and an inherent faith, particularly in rural areas, in "natural things", also complement the desire of large sectors of the population to use medicinal herbs for therapeutic purposes.

It has often been stated, mistakenly, that people prefer herbal medicines because these are cheaper. My own impressions, based on the study of the use of herbal medicines in India, China, Thailand, Sri Lanka and Myanmar, lead me to believe that cost is not a major reason as to why people prefer, in many cases, to go first to the traditional medical practitioner for herbal medicines. One sometimes reads statements that 80 per cent of the 4 000 million inhabitants of the world rely on herbal medicines for their first kind of health care because they cannot afford allopathic medicines. This may not be a correct assessment of the actual situation. Many of those persons now using herbal medicines would continue to use these even if the prices of allopathic medicines came down.

To the far-sighted, enlightened administrators in countries in the third world, this faith of the population in traditional medicine and herbal remedies

is an asset. Harassed as they are, in many of these countries, by the reluctance of doctors to go out into the rural areas and far-flung outposts of the health services, and troubled by the constant shortage of medicines, this tremendous faith in traditional medicine, the availability of medicinal plants and accessibility to the traditional practitioner in the community itself can help to increase the number of people for whom health care can be provided.

One must also keep in mind that many people in Europe, the United Kingdom and the United States of America are turning to alternative medicine – to some extent because of the side-effects induced by powerful, synthetic, allopathic drugs. Herbal medicine is one of the alternatives people are turning to.

Herbal remedies will be with us for a long time. It is therefore important to bring the use of these remedies into an existing framework of rational scientific use of medicines. It will be useful to consider what regulatory and legislative control needs to be exercised on the use of herbal medicines. Linked to this are issues of quality control, both of the raw material and of the finished product, and of standardization of herbal medicines. The need or otherwise for carrying out studies into the clinical efficiency of every herbal remedy used, to determine whether these are actually effective, is an issue that also needs to be discussed. There are several issues related to the use of herbal remedies at the primary health care level which are relevant: who will provide the medicines, how will these be obtained, and where will they be stored? Finally, there is the important question as to what type of research needs to be carried out if new medicines are to be discovered from medicinal plants. Several of the very important and useful medicines we use today come from plants. Many of these have now been synthesized and the synthetic drugs are used. In other instances, it is easier to obtain the medicines from plants even if these can be synthesized. Some of these medicines are ephedrine, morphine, quinine, emetine, reserpine, digitalis, ergot and vincristine. In recent years, no important drugs have been discovered from plants. What, if anything, needs to be done to ensure that we are creating optimal conditions for the discovery of new remedies from medicinal plants? These are the issues and questions which will be discussed in this book.

Chapter 2
A WEALTH OF MATERIAL

THE author was asked to take part in a press conference on the closing day of the Fourth World Congress of Clinical Pharmacology in Mannheim, Germany, in 1989. The main interest of several of those present was to know how to select plants for study in Germany. There are so many plants used for so many conditions in different countries of the world. One is reminded of the episode in Ramayana, the ancient epic of India when Lakshman was wounded and fell unconscious. Hanuman was sent to bring a medicinal plant, *Sanjivabuti,* from the sub-Himalayan ranges where medicinal plants grow. On arriving there Hanuman found so many medicinal plants that he did not know how to identify the one needed. He did what he thought was best – he lifted the entire mountain range and brought it to the battle field. The attending physician found the plant needed and treated Lakshman, who arose and went back to battle and triumphed over Ravana.

It is true that literature is replete with plants reported to cure different types of illnesses. This is complemented by the actual use of several hundreds of plants which are never mentioned in literature. There is undoubtedly a wealth of material. Scientists who are interested in carrying out research on medicinal plants and doctors keen to use such plants for therapeutics do not know where to begin. In the chapter on research, a list of thirty plants has been given. These are plants which have been selected as ones that deserve to be looked at well by researchers.

Any list of plants, however, can only be of limited help to the scientist, the clinical investigator or the public health administrator. They have certain interests and the plant selected for work will be influenced by these interests. While in Chandigarh, our group was interested in contraception. We were informed that in the very interior of Bihar social workers, and doctors working with them had found widespread use, in the community, of the plant known

as Banjhauri. An old woman, Paro Devi, used to administer one whole shrub to a woman within three days of childbirth, and this resulted in irreversible sterility. A search in literature for the possible effects of *Vicoa indica*, the plant, did not indicate any biological effect. After months of further thought and visits to the actual place of use, it was decided to go into the detailed endocrine effects of the plant. With considerable support from different agencies but largely from the Family Planning Foundation of India, the study was started. Paro Devi helped our plant collection team to select the shrubs according to the size of the leaf and other characteristics - she would point to ones which would act and to others which would not act. Years of study, a lot of time, considerable resources, including the establishment of a ward for clinical evaluation of Banjhauri, supported by the Council of Indigenous Medicine, went into the investigation of this plant which had not been mentioned in any scientific paper nor commented upon by any writer, explorer or missionary. The results obtained with the plant showed interesting activity in primates, lack of toxicity but disappointing results in women. This may have been because the plant could not be tested in the same condition as was being used. It should, in fact, have been tested on postpartum women and the whole shrub should have been administered with black pepper. It was, for ethical reasons, not possible to carry out the trial in the setting of the hospital in Chandigarh. The shrub itself may have lost some activity after collection – during storage – and it may be that freshly collected shrub is needed. The experience is mentioned because this one decision to go into this plant committed fifty per cent of the time of our group to this one plant. Whether we were unlucky or whether we were before our time remains to be seen.

Organizations like the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) are very much interested in plants to be used for the treatment of childhood diarrhoea. These would replace the use of powerful synthetic drugs and complement the use of oral rehydration therapy. In this case, it would be a paediatrician who would finally decide if a particular plant could be studied. One such very commonly used plant is *Eonymus kachinensis* growing in the Kachin hills. The leaves are chewed for the treatment of diarrhoea by both children and adults. This would prove to be a very useful addition of a medicine (which could certainly be used for primary health care) in places where there are no doctors. Some scientist or public health administrator will have to decide whether to test this plant or not.

Scientists or doctors in the Western world will not be interested in a cure for diarrhoea or amoebiasis but would be very interested, perhaps, in a plant which would protect the liver, particularly from the harmful effects of alcohol.

These persons would then be interested in the plant *Piccrorhzia kurroa*, which has shown very interesting liver protective effect in experimental studies and certainly deserves further clinical evaluation.

A national medical research council will have its own criteria to be used for supporting research on medicinal plants. The Indian Council of Medical Research, after years of keeping away from supporting research on plants, has recently returned to selectively support research on the use of medicinal plants for what is termed the following "refractory" conditions – anal fistula, filariasis, urolithiasis, viral hepatitis, bronchial asthma and diabetes mellitus. We have here an interesting approach to selecting plants for further research. The disease is identified first from a national perspective, and then plants are selected for being tested in these conditions. The broad criteria adopted by the Council has been widespread prevalence of these conditions, lack of an effective cheap remedy for these conditions in the allopathic system of medicine and the chronic nature of the disease. The plants selected for trial have been selected because there is a rationale available for the use of the plant – either it has been mentioned in literature or it is actually being used – and easy availability of the plant. There is hardly any point for scientists in India to evaluate for its beneficial effect on arthritis, for example, a plant that grows only in South America. It is interesting to note, however, in passing, that when the national authorities of a country planned to sterilize a whole race in recent years, the plant chosen for being baked in bread to induce irreversible sterility was a South American plant. Fortunately, as correspondence in the archives indicates, the plant material did not arrive in time for such a heinous experiment.

The whole world recognizes the need for family planning. The countries where there is utmost need, such as China and India, have had, for long, successful or not so successful programmes. Developed countries, only marginally interested till now, are coming to realize that the environment cannot be protected until the global population on the planet is limited. There are several methods of practising contraception but an easy method is still not available. In the tribal population in Phulbai district in the State of Orissa in India, the roots of the plant *Plumbago rosea*, mixed with alcohol from the plant *Madhuka indica*, is used as a self-administered, oral post-coital contraceptive. Such a preparation would add to the contraceptive technology available today. Further investigation of a plant such as *Plumbago rosea* – known in literature to be toxic, which is what one could expect - would need to be carried out by a group interested in contraception research supported by the national government or a body such as WHO. It may interest the reader to know that a small effort was made by a group to grow this plant in Bhubaneswar, capital of Orissa, so that this plant could be used for further

study. The author was gratified that this proved impossible; so popular was the belief in the plant and so much perhaps the need that after the plants grew to a certain stage, they disappeared. One word of caution, however, to any reader who would like to test the plant – the alcohol from *Madhuka indica* may be very important, either in releasing the early anti-fertility activity or in blocking the toxic effect of the plant. A second note of caution – the roots have to be taken freshly uprooted. The discovery of gossypol and the present status in its use will be dealt with in the next chapter. Chinese scientists, however, have just published very preliminary results which suggest that the plant *Tripterygium wildfordii* could also be investigated further for use as a contraceptive for men. It has been used for long in China for treating arthritis. Scientists will have, at some time, to decide whether effort and resources should be put into the work needed for studies – experimental and clinical – to study this plant further.

It is not too early to think of plants which are known to enhance the immunological responses in humans. Such a plant substance would be of value in the treatment of Acquired Immunodeficiency Syndrome (AIDS) and complement other drugs being developed to delay the development of the disease in those already infected. The Chinese plant, *Trichosanthen,* and the Indian plant, *Tinosporia cordiofolia,* are two plants which could be of value in AIDS and need to be investigated further. There are several other plants thought to strengthen the host's defence mechanisms.

Although there is a wealth of material available, selection has to be made based on needs, the interest of the researcher, needs of a national authority and the thinking of the pharmaceutical company, which, hopefully, would select one or two and investigate them. However, it could also be possible that these promising plants will never be tested. It has been years since we came to know of the use of the medicinal plants used by the Amazon Indians but nothing has been done. Among the interesting plants, Maxwell saw being used beneficially were *Croton salutaris* for stemming bleeding, a species of *Phyllanthus* for dissolving renal stones, *Chlorophora tinctorea* for treating toothache, an *Alchornia species for treating arthritis and the plant Cyprus corymbosis for preventing* birth. Another plant used by the Xovantes Indians is a species of *Desmodium.* It is used in the same way as the plant *Vicoa indica* is used in the interior of Bihar in India. The whole shrub is used for preparing the infusion.

Public health administrators of a country interested in using a limited number of useful herbal remedies for health care at the first level will have their own criteria for preparing such a list. Their criteria will perhaps be: (a) availability of the plant in the area so that it could be readily used; (b) belief in the value of the plant as

otherwise the people will not use it, and (c) some information in literature perhaps that the plant is effective for the conditions it is used for.

It will be interesting to look at some of the lists of plants prepared for use at the primary health care level as this will give us an idea of the great variety of plants available and used in different parts of the world.

The Primary Health Care project attached to the Medical Faculty at Varanasi University, India, has carefully selected plants which could be used in different conditions. This list (Table 1) makes interesting reading and is presented as it has been published by the Varanasi project and presumably the efficacy of these plants for the conditions listed will be tested. What is interesting is that of all the plants available, a selective list has been prepared.

The Eastern Mediterranean Regional Office of WHO organized an Intercountry Meeting on Use of Medicinal Plants at the Primary Health Care Level in Kuwait from 20 to 25 April 1985. The Minister of Health in Kuwait, H.E. Dr A.R. Al Awadi, inaugurated the meeting by referring to the rich heritage in the use of medicinal plants and herbal remedies described in Arab medicine and felt that there was no need to use synthetic drugs when simple herbal remedies were available and had been used for centuries to cure common conditions. The Regional Director of the Eastern Mediterranean Region, Dr El Gezairy, in his message stated that several countries in the Region had been, and still were, using medicinal plants for health care. He also felt that it was important to ensure that this heritage should be employed to the full and utilized most effectively for the alleviation of sickness and suffering.

One main objective for the participants, representing seven countries of the Region, was to identify a core list of medicinal plants to be used at the primary health care level. There were representatives from Afghanistan, Egypt, Kuwait, Pakistan, Saudi Arabia, Somalia and Sudan. The representatives of the countries, all using herbal medicines, identified twelve conditions encountered at the primary health care level for which herbal remedies could be used. These conditions are:

- Gastrointestinal diseases
- Respiratory diseases
- Skin diseases
- Helminthic infestation
- Fever
- Pain and inflammation
- Allergy
- Urinary tract infection

Table 1. *List of plants prepared by Varanasi University for use in PHC*

Plants for promoting health (immunity)

Ocimum sanctum
Sida cordifolia
Abutilon indicum
Withania somnifera
Terminalia arjuna
Embelia officinalis

Plants for care of the mother

Asparagus racemosus
Saraca indica
Cynodon dactylon
Curcuma longa

Plants for care of infants and children

Acorus calamus
Centella asiatica
Bacopa monniera
Convolvulus pluricaulis
Piper longum
Phyllanthus niruri
Terminalia bellirica
Zingiber officinalis
Butea monosperma
Embelia ribes

Plants for promotion of nutrition

Daucus carota
Moringa oleifera
Citrus medica
Cicer arietinum
Phaselus aurcus
Tritcum sativum
Bauhinia variegata
Trachyspermum ammi

Plants for family planning

Hibicus rosa-sinesis
Vitex nigundo
Embelia ribes

Plants for common diseases

Aegle marmelos
Terminalia chebula
Azadirachta indica
Caesalpinia crista
Albizzia lebeck
Tinosporia cordifolia
Eclipta alba
Adhata vasica
Aloe vera
Andrographis paniculata
Psoralea corylifolia
Holarrhena antidysenterica

Plants for infectious diseases

Malaria
Caesalpina crista
Alstonica scholaris
Swertia chirata

Filariasis
Streblus asper

Tuberculosis
Pueraria tuberosa

Leprosy
Achyranthes aspera
Centella asiatica

Plants for systemic disorder

Diabetes mellitus
Pterocarpus marsipium
Eugenica jambalana
Momordica charantia
Gymnema sylvestre

Hypertension
Rauwolfia serpentina

Ischaemic heart disease
Terminalia arjuna
Commifera mukul
Inula racemosa
Saussurea lappa

Bronchial asthma
Albizzia lebeck
Solanum xanthocarpum
Glycyrrhiza glabra
Adhata vasica

Peptic ulcer
Embelia officinalis
Eclipta alba
Glycyrrhiza glabra
Asparagus racemosus

Infective hepatitis
Andrographis paniculta
Phyllanthus niruri

Impotency
Mucuna pruriens

Cancer
Semecarpus anacardium

Injury (Fracture)
Crissus quadrangularis

Stones and urinary tract infection
Crataeva nurvala
Tribulus terrestris
Boerhavia diffusa

- Arthritis conditions
- Eye diseases
- Burns, scalds, wounds, abscesses and swellings
- Snakebites, scorpion stings and insect stings.

The criteria for the selection of plants for each of these conditions are:

(1) Actual use of the medicinal plants in the countries of the Region.

(2) Scientific literature indicating efficacy of the plants in certain diseases and common conditions.

(3) Mention of the plants in early texts of Islamic scholars as having therapeutic effect.

(4) Use of medicinal plants for therapeutic purposes in countries outside the Region.

The participants expressed the view that the list was only a model list for the Region and should be modified by every country to meet its own requirements. This list is given in Table 2.

In any discussion on the selection of plants, either for further research or for use, there are three issues which need to be gone into.

The first is that specific plants are used for specific use in some countries and cultures but the same plants are not used for that specific activity in another country even though the plant is available in both the countries. The two lists of plants prepared for use at the primary health care level – one by Indian researchers and one by the Arab countries – clearly indicate this.There could be two reasons for such a difference. The first possibility is that the same plant, in different environs, does not possess the same activity as the active alkaloids or steroids are reduced or increased according to the environs and influence of other factors such as weather, humidity and soil condition.

The second line of thought is that the plant does, in fact, possess that activity, albeit perhaps in lesser quantum, but that this beneficial therapeutic effect has just not been discovered. The author believes that both these possibilities are in fact realities and that is why research for medicinal plants has been so frustrating.

The plant *Artemesia annua* was reputed to possess antipyretic properties and, as has now been demonstrated, antimalarial activity in China, but in neighbouring countries, such as India, do not have that antipyretic/antimalarial activity or, if it has it, it has it at very low strength. It may, because of mutation,

Table 2. *Model list of plants*

Gastrointestinal tract remedies

Anti-diarrhoeals
- Acacia arabica
- Acacia catechu
- Berberis aristata
- Commitfera mukul
- Punica granutum

Laxatives
- Aloe ferox
- Cassia acatifolia
- Chicorium intybus
- Glycyrrhiza glabra
- Plantago ovata, P. psyllium
- Rhamnus frangula
- Ricinus communis

Carminatives
- Cinnamon zeylancium
- Elettaria cardamomum
- Matricaria chamomile
- Mentha spp.
- Ocimum senctum
- Origanuni spp.
- Thymus vulgare
- Umbelliferous fruits, anise, carraway
- Coriander, cumin, dill and fennel
- Zingiber officinalis

Spasmolytics
- Atropa belladona
- Datura spp.
- Hyoscyamus spp.
- Solenestemma argel

Stomachics
- Rheum officinalis

Anti-emetics
- Atropa belladona
- Hyoscyamus spp.
- Mentha spp.
- Zingiber officinalis

Remedies for upper respiratory diseases
- Adhata vasica
- Allium cepa
- Althea officinalis
- Ammi visnaga
- Cassia fistula
- Cinnamonum zeylanicum
- Ficus carica
- Glycyrrhiza glabra
- Hibiscus sub darrifa
- Linum visitatissmum
- Mentha spp.
- Nigella sativum
- Ocimum sanctum
- Prunus domestica
- Psidium guarjara
- Tilia tomentosa, T. ulmifolia
- Urginea maritima
- Zingiber officinalis

Remedies for skin diseases
- Aloe vera, A. herbadnse, A. ferox
- Ammi majus
- Azadiracta indica
- Ficus carica
- Fumara officinalis
- Lausoria alba
- Lupinus termis
- Matricaria chamomillae
- Nymphaea alba
- Santalum albam

Anthelmintics
- Albizia anthelmintica
- Artemesia cina

Antipyretics
- Allium cepa, A. sativum
- Fagonia arbica

Analgesics and anti-inflammatory agents
- Lactuca sativa
- Matricaria chamomile
- Peganun harmala

Anti-allergics
- Cydonia oblonga
- Zuzyphus vulgaris

Remedies for urinary infection
- Ammi visnaga
- Balantis aegyptiaca
- Cucumis sativum
- Cympopogon proximus
- Nymphaea alba
- Raphanus sativum

Remedies for arthritic conditions
- Capsicum minimum, C. annum
- Commifora mukul
- Withania somnifera

Remedies for eye diseases
- Berberis aristata
- Rosa domascena

Treatment for burns, scalds, wounds, abscesses and swellings
- Aloe vera, A. barbadense, A. ferox
- Lawsonia alba
- Lenium usitalissium
- Punica granutum

Treatment for snakebites and scorpion and insect stings
- Aloe spp.
- Azadiracta indica
- Heliotropeum stringosum

have totally lost that property. This could be the explanation in this case. However, that explanation is not perhaps the reason why *Eunymus kachinensis* possesses, or is reported to possess, antidiarrhoeal activity and is being used for this purpose by people in the Kachin hills while in the neighbouring hills in India, there is no such belief, nor use of the plant. In this instance, it is probable that this antidiarrhoeal property of the leaf of *Eunymus kachinenis* has not been discovered in its Indian counterpart because it has not been looked for. This is particularly true if there is no mention anywhere in existing literature about this particular property of the plant. While travelling through Myanmar, it was pointed out to the author at several places that a soup made of the leaves of a plant *Morinda augustofilia* would certainly induce secretion of milk in nursing mothers who do not have adequate milk. This has however been barely mentioned in a book on *Medicinal Plants of Myanmar*, brought out by the Department of Agriculture and Forests. This property of the leaves of *Morinda augustofilia* has not been mentioned, as far as the author is aware, in any book on medicinal plants in India, Sri Lanka, Thailand or the Philippines. Again, in this instance, it is felt that the property would be present in this plant in other countries but has not been discovered.

It will be interesting, in pursuing this line of thought, to have a look at plants which are thought to induce an aphrodisiac effect in different countries. The discovery of such a plant and its legitimate use after regulation would prevent indiscriminate slaughter of wild life, such as rhinoceroses for its horn, seals for their glands and hundreds of other species of animals. Twenty-eight plants that grow in the Philippines, Sri Lanka, India and Myanmar and are reported to induce an aphrodisiac effect in men are listed in Table 3.

Table 3. *Plants reported to induce aphrodisiac effect*

Acorus calamus	Magnoliamine
Aleurites moluccana	Magnolia fuscata
Costus speciosus	Ipomoea mauritania
Strychnos nuxi vomica	Semecarpus anacardium
Ceiba pentandra	Asparagus racemosus
Artocarpus heterphyllus	Mucuna prurita
Piper betle	Boerhaavia diffusa
Pandanus amaryllifolius	Marranta aruninacea
Arecha catechu	Canna edulis
Erytroxylon cocoa	Butea superba
Okhra	Asaragus officinalis
Avacado	Dioscore triphylia
Anacylus	Piper longum
Pyrethrum	

It is very interesting to note that out of all these plants, only four have been mentioned in at least three of the four countries. These are the seeds of the *Mucuna prurita pruriens*, the roots of *Ipomoea mauritania*, the roots of *Costus speciosus* and the leaves of *Piper betle*. Since resources are always limited and since the cost of developing one plant drug will be approximately $ 5 to 6 million, as against $ 100 million reported, for example, to have been spent by a pharmaceutical house in developing a new synthetic drug released for the treatment of migraine, it is important to decide whether the use of a plant in more than one country means that the plant is effective. On the other hand, reported activity from one country, for one plant, if true, is all that is needed. However, a choice has to be made. This is where the experience, background, judgement and "feel of the field" sense of the investigator or group of persons making the selection is so important. Readers interested in knowing more about these plants should refer to the following:

Handbook of Philippines Medicinal Plants, Vol. IV (1986)
Medicinal Plants used in Sri Lanka, Vol. 1-4 (1982)
Medicinal Plants of India, Vol. 1 and 2 (1976)
Medicinal Plants of Myepadetha (1985)

A look at the plants used for the treatment of snake or scorpion bites in neighbouring countries, such as India, Myanmar, the Philippines and Thailand, again reveals differences. The plants commonly used for treating such bites in India are:

- Leaves of *Andrographis panticulata*
- *Roots of Gloriosa superba*
- Leaves of *Tephrosea purpura*
- Roots of leaves of *Achyranthes aspera*
- Roots of *Aristolochia indica*
- Seeds or roots of *Crotolaria laburnifolia.*

The plants used for this purpose in Myanmar are the following:

- Harrisonia perforata
- Leela aspera
- Ruella tuberosa

The plants used for counteracting snakebites in Thailand are:

- Clinacanthus nretanus (red flowers)
- Barleria lupulina (yellow flowers)

More good clinical trials are needed to assess the possible efficacy of plants in counteracting the effects of snakebite. Animal studies could be carried out to study the effect of these plants on animals administered snake venom. One such interesting study has been carried out. Pterocarpans and Carbenagrins A-I and A-II, isolated from a plant used to treat snakebites in Brazil, when administered to animals, counteracted, within thirty minutes of administration of the venom, the hypotensive effect of the venom as also cardiac and respiratory arrest induced by the venom. The aqueous extract is obtained from the roots of the plant *Cabeca de Nagra.*

The second issue which needs to be discussed is the relevance of a plant being in use over centuries. There are plants which have been mentioned in ancient texts of Indian and Chinese medicine, 2000 to 3000 years ago, as possessing medicinal properties. Some of these plants are not used any more and have been discarded while others such as *Commifora mukul* and *Boerhaavia diffusa* are still being used at this time. It has been said that those plants still being used today, which have stood the test of time, are more likely to be effective because, if these were not useful or were toxic, they would have been discarded. This argument for natural selection needs to be examined carefully. It would be too simple to conclude that ineffective or toxic plants have been discarded and the useful plants have remained in use. It may be that a plant was useful and effective but that cultivation of that plant could not be sustained due to economic factors. A plant which was therapeutically effective may have undergone mutation and become therapeutically ineffective due to ecological or environmental factors.

The third issue deals with the assessment of pharmacological and clinical pharmacological results when looking at the results of such studies and deciding whether to select a plant for further work. It is important to keep in mind that results obtained in animal studies are not always predictive of what could happen in man. A plant extract, ineffective in animals, could still be effective in man, and there are several examples of efficacy shown in animal models for synthetic compounds which do not act on man. This is true of both synthetic compounds and plant substances. Whether the variation is seen more in plants is not known.

In the past, testing for pharmacological and therapeutic activity has been carried out by the traditional extraction and animal model approach. This may be inappropriate for about half the plants known to have a beneficial effect. Such results, obtained in inappropriate methods, should not be discarded when selecting a plant for further work because it is not the plant which is ineffective but the methods used which were ineffective. It would, for example,

be unwise to discard investigation of the plant *Momordica charantica* for the treatment of diabetes because the traditional model did not help. The plant extract has to be tested whole to be effective as a freshly prepared extract.

It is hoped that this section has highlighted some of the factors to be kept in mind when selecting a plant for further study. Eventually, the selection will depend on the interest of the investigator. A cardiovascular research pharmacologist may choose to work on *Terminalia arjuna*, a reproductive endocrinologist on *Plumbago rosea*, a rheumatologist on *Curcuma longa* and a malariologist on different types of artamesinin. A person interested in the behaviour of cats will probably study the effect of the plant *Acylypha indica* which, when planted, is reputed to exert a specific effect on feline behaviour.

It is important also to test the plants in the manner it was used. This is not always possible but, as far as is possible, it should be done. Thus, when King Mindon of Ava was given every day the plant in use for 2000 years, *Boerhaavia diffusa*, it was given to him mixed with honey, the flowers of *Morunga oleifera* and coconut. If we rush to test the effect of only *Boerhaavia diffusa* for its effect on the quality of life, we are not testing the plant in the proper way in which it was used.

Chapter 3
RESEARCH

THERE was consternation in the village of Wang in Nanching province of the People's Republic of China in the 1940s because no babies were being born in that village. The village elders felt that the women of Wang were infertile and sent their young men to neighbouring villages to bring back brides so that families could have children and grandchildren. There was however still no joyous sound of crying babies in the village. The village elders thought that the young women from neighbouring villages could not bear children either. More young men from Wang were sent to still further villages and asked to marry young widows with children and bring back these wives. The young men agreed and dutifully brought back their wives and step-children. And yet no babies were born in the village of Wang. For full ten years not a baby was born in this village. A visiting government chronicler passing through Wang noted this fact and also mentioned, among other things, that the villagers of Wang were so poor that they could not even refine the cotton seed oil they were using for cooking. In the 1950s babies started appearing in the village – the curse upon the village had passed. During this time the standard of life in Wang, as in other parts of the country, had improved. This fact was carefully recorded by another government chronicler who noted that the villagers did not use, any more, cotton seed oil for cooking but were now using soyabean oil as the cooking medium.

The apparent relationship between the use of cotton seed oil and the absence of babies in the village of Wang was noticed by a research worker, who concluded a paper in 1957 with the words "My proposition is based on this observed fact. It seems that cotton seed oil can be used for birth control. The fact that when stopping eating cotton seed oil the birth control effect automatically disappears shows that it is most economical, convenient

and natural". Nothing very much happened and this observation was buried in the many publications on the use of medicinal plants.

Chronic bronchitis is a big problem in China in the winter. It had been stated in the early texts of Chinese medicine that cotton seed oil cured bronchitis. An investigator in the 1970s sought to evaluate the effect of cotton seed oil on patients with bronchitis by carrying out a controlled clinical trial. His subjects were five men. In addition to observing the effect of cotton seed oil on bronchitis, he also studied its effects on some other systems of the human body. One of these systems was the reproductive system; he ticked off the tests to be carried out and included examination of the sperm count as one of the tests to be carried out.

The cotton seed oil was administered to five men. It was observed that four of these men had a very low count of sperms in their semen after taking the oil - a condition known as azoospermia while the sperms in the fifth were dead - a condition known as necrospermia. None of these five men would have been able to father an offspring.

Gossypol has usually been administered at a daily dose of 20 mg for 75 days followed by 50 mg once a week. Gossypol itself may not be the actual contraceptive to be eventually used by man and an analogue or another substance may prove better. However, the emergence of gossypol as a potential male contraceptive from China shows what is possible and what could again be repeated in the future.

A Sanskrit text on Ayurveda, the ancient Indian system of medicine, the *Sushruta Samhita, written in the year 600 BC, noted that the plant Commifera mukul* was useful in the treatment of obesity and in conditions which were equivalent to what we describe today as hyperlipidemia or increased concentrations of cholesterol in the body. This plant has been used by practitioners of the Ayurvedic system of medicine for at least 200 years and perhaps throughout the centuries since the text, Sushruta Samhita, was written nearly 2600 years ago. The first appearance of this plant in modern scientific literature was in a thesis published by G.V. Satyavati in 1966 from Varanasi in India.

It was shown that crude gum guggal, obtained from the plant *Commifera mukul,* significantly lowered the serum cholesterol level in rabbits which had a high cholesterol level - induced by feeding. It was also shown that this plant substance protected rabbits from cholesterol-induced atherosclerosis which, in common terms, means a hardening of the arteries. This was followed by pharmacological and toxicological studies on the plant *Commifera mukul*

and clinical evaluation of the same to determine whether the plant substance acted also on humans and whether any side-effects were observed after using guggulipid. The results showed that guggulipid was effective in humans and no particular side-effect was associated with its use. Approval was obtained from the national drug regulatory authority in India for carrying out further clinical trials with the drug, and eventually, for marketing the drug in India. After about twenty years from the first observation on rabbits the drug has been marketed in India and other countries for its beneficial effect in reducing cholesterol levels in patients with raised levels of blood cholesterol.

Malaria is once again a very great problem in many countries of the third world. One of the many difficulties in the management of malaria is the emergence of resistant strains of malarial parasites to the antimalarial drugs now available. In many of the countries, there is danger from a type of malaria known as falciparum malaria, which is resistant to chloroquine, the commonly-used antimalarial drug most widely used. However, this drug does not act in these cases of "cerebral" malaria resistant to chloroquine when the patient becomes unconscious and finally succumbs to the disease. The only drug which can be used is the old medicine, quinine, which causes many side-effects. Having only one medicine to treat a particularly serious condition is also not satisfactory as there will always be some patients who do not respond to quinine and who need another drug. Till recently, there was no such other drug. Chinese researchers first found mention of the use of the plant *Artemesan annua* in a Handbook of Prescriptions for Emergencies, the Zhouhou Beijfang, written 1000 years ago by Ye Hong for a clinical condition surmised to be malaria. The Chinese name of the plant used is quing hao tsu, and it is stated clearly in that book that the quing hao tsu extract is prepared, not by the usual boiling procedure, but by steeping and wringing out the plant and using the juice. The condition for which this was used appeared to the Chinese investigators to be akin to malaria characterized by high fever and rigor.

Chinese scientists at the Institute of Chinese Traditional Medicine collected the plant and carried out, as suggested in the book written 1600 years ago, a slow low temperature extraction procedure. They then isolated the active principle. With this beginning scientists and clinical investigators carried the work all the way through to synthesis of artemesinin and to its clinical evaluation as an antimalarial agent. It was found to be effective in cases of falciparum malaria resistant to chloroquine.

A second antimalarial, in addition to quinine, is now available to the world in serious cases of cerebral malaria resistant to chloroquine. Other analogues of artemesinin are now being evaluated and it looks as if these arteether and artemether analogues may be more effective than artemesinin. A whole new area in herbal medicine therapeutics has been thrown open by this discovery in addition to a new valuable medicine having been introduced into Western medicine from the heritage of medicinal plants possessed by countries such as China and India.

The successful introduction of three plants into modern therapeutics and family planning in the last 40 years indicates that there are other discoveries waiting to be made. There are, undoubtedly, many other plant substances which could be used in our modern systems of medicine. Some of these plants are being used today by practitioners of the traditional systems of medicine in the third world and by herbalists in other countries. Other substances may not be in use today but their use is perhaps mentioned in the ancient texts of Chinese, Ayurvedic and Unani systems of medicine. The rich heritage available to man needs to be explored further. The fact that only three or four plants have been introduced for use in modern medicine after years of work does not mean that there are no more drugs to be discovered. It means that the approach used and the constraints present have prevented us from obtaining information and knowledge about medicinal plants which would have helped us to treat several illnesses for which we do not have medicines or have medicines which are themselves toxic to the patient.

These problems and constraints will be dealt with later when discussing the fashioning of a strategy that could be more effective. Before that it is necessary to discuss which plants show most promise of future development as drugs. There are hundreds of plants reputed to be effective in many different conditions. If research is to be carried out on certain medicinal plants, then the plants should be carefully chosen. In this section of the book, a selection of those plants which today show most promise has already been made to help the scientist and the clinical investigator in deciding which plant to select for study. Thirty such plants have been listed below. The indication for which use the plant should be clinically evaluated has also been given. Since nearly all of these plants are in use today, clinical evaluation can be undertaken after minimal experimental toxicological studies. Extensive animal toxicity studies are not needed. These plants are listed in Table 4.

Table 4. *Plants for possible study*

Picrorhiza kurrooa (Handa and Kapoor 1989)	To protect liver
Terminalia arjuna (Handa and Kapoor 1989)	In cardiovascular disease
Moringa oleifera (Medicinal Plants of India, Vol. 2, 1987)	In hypertension
Curcuma longa (Handa and Kapoor, 1989)	As an anti-inflammatory agent
Andrographis paniculata (Handa and Kapoor, 1989)	To protect liver
Ocimum sanctum (Handa and Kapoor, 1989)	To treat cough
Centella asiatica (Handa and Kapoor 1989)	To improve the quality of central nervous system responses
Daucus carotus (Medicinal Plants of India, Vol. 1, 1976)	To prevent implantation and as a contraceptive
Plumbago rosea (Medicinal Plants of India Vol. 2, 1987)	To prevent implantation and as a contraceptive
Artemesia annua (Handa and Kapoor, 1989)	To treat malaria
Dichroa febrifuga (Medicinal Plants in China, 1989)	To treat malaria
Xanthium strumarium	To treat malaria
Phyllanthus amarus (Medicinal Plants of India, Vol. 2, 1987)	To protect liver
Albizzia lebeck (Medicinal Plants of India, Vol. 1, 1976)	To treat asthma
Adhatoda vesica (Handa and Kapoor, 1989)	In respiratory problems
Ancistrocladus heyneanus (Medicinal Plants of India, Vol. 1, 1976)	In dysentery
Croton oblongifolius (Medicinal Plants of India, Vol. 1, 1976)	For gastric acidity
Azadirachta indica	As an anti-inflammatory agent
Nyctanthes arbotristis	In leshmaniasis
Streblus asper (Patnaik and Dhawan, 1986)	In filaria
Hamiltonia suaveolans (Patnaik and Dhawan, 1986)	In diabetes
Gymnema sylvestre (Medicinal Plants of India, Vol. 1, 1976)	In diabetes
Momordica charantia	In diabetes
Withania somniferum (Handa and Kapoor, 1989)	To improve quality of life
Boerhaavia diffusa (Handa and Kapoor, 1989)	To improve quality of life
Tinospora cordifolia (Patnaik and Dhawan, 1986)	To improve quality of life
Asparagus racemosus (Handa and Kapoor, 1989)	To improve quality of life
Tripterygium wilfordii	Male contraceptive
Bacopa monniera	To improve the quality of life
Hibiscus rosasinensis	Female contraceptive

These plants have not been selected subjectively purely because of long experience in this field. These have been selected on certain criteria which are given below. These criteria were not used for the purpose of scoring but formed the framework which was used for this exercise.

- Names of plants given in ancient textbooks of Chinese, Indian and other systems of medicine.
- Natural selection of plants which were mentioned in ancient texts and which are still in use today.
- Names of plants given in early writings of explorers, missionaries and writers and in writings of herbalists.
- Plants that are actually being used today even though no mention has been recorded earlier.
- Results of research carried out with plants – experimental or clinical. These comprise both published papers and unpublished work.
- Condition for which the plant is to be used.

The last criterion needs some clarification. It is the author's suggestion that research should be carried out to determine whether plants could be used in certain diseases such as liver disease, bronchial asthma and arthritis. There is hardly any point in trying to introduce a herbal medicine for the treatment of infection, cancer or acute respiratory infections. This thinking has also influenced the selection of plants for inclusion in this list. There are several plants which have been used for centuries for increasing the quality of life. Five of those included in this list have been mentioned in the ancient texts of traditional medicine and are also widely used today. There is no reason why clinical evaluation should not be carried out to assess whether these plants do, in fact, enhance the quality of life since methods for assessing the quality of life are being developed. These are not plants reputed to have aphrodisiac properties.

It is expected that if these 30 plants are looked at carefully, there would be at least two or three important additions to therapeutic armamentarium of modern medicine. At least half a dozen more of these plants could perhaps be used more effectively for first-level primary health care. This hope will not, however, be realized unless there are major changes made in our approach to research on medicinal plants. If these changes are not made and if medicinal plants research is carried out in the next 25 years in the same way as has been done for the last 25 years, then it is extremely doubtful if any discovery will be made at all. These changes, which will be discussed below, are not

easy ones to make and means long-term planning. It is doubtful, in fact, if such changes will be made at all. The prospects for medicinal plants research today is depressing.

The following far-reaching changes will have to be made if we could to carry out successful research on medicinal plants leading to new drug development:

- Attracting the best brains to this field of work
- Use of appropriate methods and new technology
- Development of infrastructure
- Training of pharmacologists and clinical pharmacologists in medicinal plants research
- Renewing interest of pharmaceutical houses in medicinal plants drug development.

Each of these will be considered in some detail.

Any research is only as good as the quality of the research carried out. The quality of research depends primarily on the quality of the scientists doing the research. It is unfortunate for medicinal plants research that the best minds in biomedical and clinical research have never been interested, nor are they interested now, in this field of work. An exception could however, be made for chemists who have been interested in isolating compounds present in plants and synthesizing them but have not been interested in drug development. The reason for this mediocrity in medicinal plants research is that the best potential research scientists from the third world countries where medicinal plants are being used have all been trained in the West. There was no tradition of medicinal plants research in the UK, USA, Germany or Sweden and the "best and brightest" were trained in cardiovascular pharmacology or pathology, endocrinology, autonomic pharmacology or respiratory physiology, in addition to the clinical sciences. Not one worked on medicinal plants. When they returned, they not only continued to work in the specialized area in which they were now leaders in their own countries but they drew into these fields the second line of bright persons who helped to develop a group in these areas. In their turn, these too went abroad and returned more competent in their chosen field of work which certainly was not medicinal plants research. It was left to those not selected for these "sophisticated" lines of work to go into medicinal plants research and develop their own models since no such models were available in the advanced countries in the West. This is the pattern followed by scientists and researchers in India,

Pakistan, Sri Lanka, Thailand, Myanmar, the Philippines and Malaysia – to mention a few countries in South-East Asia. A few of these scientists did go into medicinal plants research but this was never their major field of interest.

The scientists carrying out medicinal plants research were, by and large, mediocre. There were no models which could be used, there were no centres in the so-called advanced countries where training could be obtained and there was, in the early years, a certain amount of sniff of second-rate research about people involved in this area. It is therefore not surprising that the results of such research have been unrewarding. Hundreds of mediocre papers are produced every year and will go on being produced but these do not lead to drug development. A recent review, published in 1989, of the research carried out on medicinal plants in India in recent years bemoans the fact that the papers published are sometimes of poor quality, that they do not contain details such as proper identification of the plant material used, nor the place and time of collection of the plant nor the extraction procedures used. The position is even worse in respect of clinical trials carried out with medicinal plants. Unless the best scientists and research workers are drawn into this field, the quality of research will not be enhanced. As an appropriate addition, it can be pointed out, for example, that since 1947 – when India attained independence, and a thrust was made in this field – there have been six Directors-General of the Indian Council of Medical Research. Of these, three have been pathologists, one a microbiologist, one a specialist in nutrition and one a respiratory physiologist. None of these had carried out any research on medicinal plants.

The drawbacks and constraints mentioned above do not, fortunately, apply to China since it was not an "open" country till many years after the Cultural Revolution. The author was one of the first scientists privileged to visit China after the Cultural Revolution, in 1981, to take part in a clinical pharmacology training course organized by WHO in Beijing. Chinese scientists were not sent abroad for training and so their "best and brightest" did not get trained in the UK, USA and Europe in disciplines far removed from medicinal plants research. They remained in the country and some of their top brains got involved in medicinal plants research. Further, since the Chinese had to rely on themselves in all areas and struggle on their own, they developed their own models based on pragmatism and practicality, and this also helped in medicinal plants research. They tried to find solutions in their own way and they based their strategy on the three strengths nobody and no foreign power could even take away from them: (a) their own system of traditional medicine, (b) a large population providing adequate manpower, and (c) time – since they were not in a hurry and not

in competition with others. Research on medicinal plants, therefore, has always had more vitality and more strength from the soil in China than in other countries. These advantages, combined with the calibre of persons carrying out such research, augurs well for medicinal plants research in China. Further, scientists in China are not overburdened with traditional Western concepts of research methodology which have many times acted as a constraint in other countries. In the early years, for example, Chinese investigators were not so worried, as they are now, about standardization of herbal medicines; they were not very concerned about clinical pharmacological concepts in clinical trial methodology nor were they unduly perturbed about ethical aspects of clinical trials. This enabled them to go ahead and make advances and use medicinal plants both for research and for therapeutic effect. It has enabled them to put out for widespread evaluation gossypol and *Artemesia annua* while half a dozen others are on the way. In contrast, in spite of all the funding and the papers published, India has put out only one plant, *Commifera mukul* (guggulipid), in the market while the pharmaceutical industry has developed a medicinal plant which stimulates cyclic AMP (forskolin). The rest of the third world countries have not been able to introduce any plant into the market for use in Western medicine.

Before leaving the Chinese experience, it is worthwhile noting that once an encouraging lead in medicinal plants pharmacology has been obtained, Chinese scientists and the government are very good at developing a national strategy and, if necessary, a task force for rapidly following up such a lead. This has recently also been pointed out by Indian investigators who have especially cited the rapidity with which, in China, experimental results on plants are passed on to clinical investigators, who provide all support for clinical evaluation of that particular plant. The Indian investigators concluded that this strategy has paid good dividends in China and could be even more rewarding for a country, such as India, where the infrastructure needed for such studies perhaps already exists. The Chinese approach, at the moment, appears more aggressive than the approach adopted in other countries.

It is necessary now to think as to where top-level scientists involved in research on medicinal plants for purposes of drug development should work. The first point to be cleared is that medicinal plants research carried out by chemists and pharmacognosists and pharmacologists is not necessarily – and more often than not – drug development research. A lot of unnecessary misunderstanding has been created by not appreciating this. It is very often stated that chemists and pharmacologists in the developing countries have been working on medicinal plants for the last fifty years and yet no drug has

been discovered. The research was not carried out for this purpose. It was carried out because of the scientific curiosity of the investigators in the university setting where much of this work has been carried out. It enabled young scientists to work for an advanced degree on an interesting subject and enabled the junior investigator and eventually the senior guide to write a few papers and present the results at scientific meetings. Once these objectives were attained, the investigators turned their attention to other subjects for research or other medicinal plants. The chemist would be fortunate and happy if he could elucidate the structure of an active constituent in a medicinal plant. It is pointless to bemoan that such work did not result in drug development. It was not meant to do so. The leads provided by such research could be taken up by others.

With the emergence of many third world countries as independent free countries, the heritage of medicinal plants became, to some extent, a political issue. This was "our" medicine as against modern medicine which was Western medicine. As a result, more funds became available for medicinal plants research, which was applauded, and political leaders and their bureaucratic counterparts provided more support for this type of research than ever before. The quantum of work carried out undoubtedly increased but the rapid increase in the work done perhaps acted as a constraint towards enhancing the quality of research. Some countries did better than others but, by and large, except for a few national institutes and centres, it was the same investigators carrying out the same type of work but supported by much greater resources.

The inherent drawback in scientists and chemists carrying out research in the university setting is that this framework is not suitable for drug development. Very little was done to change the strategy of research or bring in new people. It is not surprising that the results of this increased research has been disappointing from the point of view of drug discovery and development.

There were some interesting experiments carried out to see whether scientists from universities and medical colleges could combine to discover drugs from medicinal plants. The Indian Council of Medical Research initiated a Composite Drug Research Scheme, which brought about some interaction between chemists, pharmacologists, pharmacognosists and specialists in the modern and the Ayurvedic systems of medicine.

An Institute for Research in Chinese Traditional Medicine was established in Beijing. Both Sudan and Ethiopia and several countries in the third world have centres for research in traditional medicine. The Central Drug Research

Institute, Lucknow, India, with its large multidisciplinary core of scientists, has always been interested in medicinal plants. These efforts enabled younger investigators to be trained, have provided interesting field of work to hundreds and have built up awareness of the problem but these efforts have not led to successful drug development. One is hesitant to say that perhaps, at least on some occasions, high-level political pressure for this type of research resulted in rapid publication of shoddy papers. The availability of resources never available before also enabled more and more mediocre persons to get on the bandwagon of medicinal plants research.

Just as universities have always been the centre of good research, pharmaceutical houses have also been the centre of drug research leading to drug development. It is important to look back and find out why the pharmaceutical industry today has largely lost interest in research in medicinal plants. It is very important to do so because if newer drugs are to be discovered for the modern system of medicine, it can only be done by the pharmaceutical industry. It is only they who have the multidisciplinary scientists needed for drug development as well as the resources needed to put into development a drug from a plant source. It is possible to identify what went wrong with their earlier experience and to avoid the mistakes in any future effort. Since this concerns the methodology used by the pharmaceutical houses, which the writer considers was inappropriate, this section of the chapter will deal also with methods to be used in any future work.

After the discovery of reserpine from *Rauwolfia serpentine*, the pharmaceutical houses went into medicinal plants research in a big way. After twenty-five years of this type of research, nearly all major pharmaceutical houses have pulled out of this field because of the disappointing results obtained by them. Perhaps the most disappointing experience was the establishment of the Ciba Research Centre in Bombay, India, in 1961 and its ultimate closure in 1989. At this Centre, the pharmaceutical house matched the development of infrastructure with the recruitment of the "best and brightest" of Indian scientists from all over the world to develop a first-rate group of scientists working closely with the immense technical know-how and back-up of Ciba (Basel) and Ciba (USA); yet with all tremendous effort, this showpiece of the pharmaceutical industry's research effort in a developing country first closed down work on medicinal plants after fifteen years and finally closed down the Centre itself. What went wrong?

Scientists at the pharmaceutical houses had achieved success in converting synthetic compounds into drugs by synthesizing a large number of compounds and subjecting these to a battery of pharmacological and biological screening

procedures. The more active compounds were then further tested for their pharmacological profile. More analogues were prepared of the most active compounds. Toxicology was carried out with the interesting compounds. A few of the compounds, based on their pharmacological and toxicological effects, were selected for further studies. This approach works well with synthetic compounds and it was only natural that pharmaceutical scientists used this basic approach when carrying out research on medicinal plants. Different extracts were prepared of the plant to be studied. These extracts were then subjected to a battery of tests. The most active extracts were fractionated further and each further subfraction tested for activity. It was hoped that, in this manner, the active principle would be isolated and tested for pharmacological and toxicological activity. If these tests were encouraging, then an attempt would be made to synthesize the compound. In the meanwhile, a patent would have been taken by the pharmaceutical house concerned.

This approach cannot be used for all medicinal plants. It is totally inappropriate for use on plants where the activity of the plant decreases on further fractionization or where two or three active substances need to be taken together for its full effect. Each plant has its own characteristics and has to be treated individually. The blunderbuss approach of fractionation and further fractionation buttressed by a battery of pharmacological tests is not the one likely to yield results with plant material. It is doubtful if, even now, the leaders of pharmaceutical research realize what went wrong and how rich dividends both for the welfare of the population and the shareholders could still be reaped by an imaginative approach. The selection of one or two plants, based on their actual use today, and concentrating only on these plants would be a much better approach than the earlier one of screening hundreds of plant extracts.

It may be of interest to the reader to know of some of the pitfalls which have to be avoided in doing medicinal plants pharmacology. The same plant at the same place may have different levels of alkaloids in different years - thus having different intensity of biological effect. The same plant at different places - even with the same altitude, humidity and rainfall – may have different concentrations of the active substance. The same local name may be used for two or three plants making it difficult when collecting authentic samples for pharmacological screening. On the other hand, two or three local names may be used for the same plant. The type and number of plants which are grown around the plant being collected influence the quantity of alkaloids in the plant and thereby its pharmacological effect. Plants sometimes need to be taken fresh if they are to be effective. Storage and transport back to the

laboratory or ward may cause the plant material to lose its pharmacological property, partly or completely. It is doubtful if plant collectors of the pharmaceutical houses or scientists at the pharmaceutical research centres kept these points in mind when collecting potential medicinal plants.

Even at the stage of laboratory and clinical testing, there are still other pitfalls which one must be aware of. It is now fairly well recognized that a medicinal plant may need to be administered with other substances in order to exert its therapeutic effect. If three plants are given together with black pepper or jaggery or honey, it is possible that every constituent in this combination has a specific effect. The second plant may be potentiating the effect of the first plant and the third plant may be preventing the toxicity of the second plant. The jaggery, honey or black pepper may be releasing the activity of the first plant. In a situation such as this it would be futile to try and determine, by pharmacological screening – in dogs or cats or rats – which plant actually possesses pharmacological activity. As we have seen, there may never be such a plant acting alone. Even if the pharmacological activity resides in one plant, it is possible that there are two or three compounds in that plant extract, which, together, induce the therapeutic activity. The approach of extraction, testing and further fractionation, which has always been used, will not help. Further extraction and fractionation will only decrease the effectiveness of all fractions rather than concentrating all the activity. It has been shown that in approximately half of the plants the activity increases as further fractionation is carried out. However, in the other half, activity decreases as further fractionation is done. Scientists at half a dozen pharmaceutical houses have spent an enormous amount of time and money trying to track down that one alkaloid which is responsible for the blood sugar lowering or hypoglycemic effect of a plant *Momordica charantia.* The fresh aqueous juice of this plant – the vegetable known as bitter gourd – is being used by thousands of diabetic patients all over the world. Yet, all attempts to demonstrate in which one compound all this activity resides have failed because the activity in all fractions gets less and less instead of demonstrating enhanced activity in one extract or fraction.

The disappointments suffered by the pharmaceutical research units and their rapid withdrawal from the field has undoubtedly been a great setback for research on medicinal plants. It is depressing, particularly when one contrasts their successes in the field of antibiotic research. However, perhaps it may be good in one way because when they return again to this field, they would be able to begin afresh, taking advantage of all the experience gained and knowledge acquired in the last twenty years. Potential toxicology of

synthetic drugs, stricter regulatory control, escalating costs and the need to carry out extensive animal toxicology (which may not be required if the plants are already being used) may also be factors for another look at plants. It is hoped that innovatively and with careful selection, some of the major pharmaceutical houses would again support research as only they truly have the infrastructure, the multidisciplinary approach, the team approach and the resources needed for developing drugs from plants. It would be still better if their efforts could be linked to university scientists and medical research workers interested in this field. Only then will new technology be used in this field. The facilities present, for example, at the Department of Plant Sciences at Oxford, would be very helpful to scientists and researchers, both at universities and research centres and in pharmaceutical houses in their quest to develop newer medicines for use from the plants around us. Development of new methods for screening has been very slow in this field and this drawback will be overcome by the linking process suggested. In the same way, institutes in the developed and in the third world could think of developing mutually-beneficial links in their research.

This may be the time to discuss possible help from international organizations, such as the World Health Organization (WHO), in support of research on medicinal plants. WHO will certainly help in developing links of the type envisaged above. WHO also has a programme in traditional medicine and the priority areas in traditional medicine research which would form the collaborative effort between WHO and the countries are decided by the countries themselves. Research on medicinal plants is a priority in research programmes in several regions of WHO and in many countries in those regions. Funds available for research however are not very large. It has often been asked whether WHO, perhaps in collaboration with the United Nations Development Programme (UNDP), the World Bank and other international organizations, would consider establishing a research institute aimed at developing drugs from medicinal plants. An International Institute for Herbal Drug Development – a single, well-supported centre staffed by top scientists all over the world working under U.N. or WHO aegis, such as the International Rice Research Institute in Manila – is an interesting idea and could be another mechanism, non-pharmaceutical in character, helping drug development. This is highly unlikely as the World Health Organization, for good and valid reasons, believes in strengthening national institutes and developing national capacity rather than in building institutions.

At one time, in the early 1970s, there were some thoughts about establishing an international centre for research in human reproduction, aimed at

contraceptive development, at Stockholm. Such a centre would have been supported by different international agencies but run by WHO. This idea did not get very far, nor the suggestions mooted at the same time for a WHO International Research Centre for Parasitology. Instead of the proposed centre, ACCORD, the Special Programme for Research and Training in Human Reproduction, was initiated. This programme still continues. In the Human Reproduction Programme, a task force was established for developing a herbal contraceptive. Research was carried out at different centres, both in the developing and the developed countries, and top scientists were invited to participate in the programme. Once again, the results were disappointing and this particular task force has been closed down. The reasons were largely (a) that the same approach of chemical extraction and animal screening was adopted, and (b) that the investigators were scattered all over the world. There is much more chance of success when all the investigators work together in a milieu of drug development and discovery temper. The only other way in which WHO or the United Nations could help would be to mobilize resources and then, at the appropriate time, pass funds on to the pharmaceuticals for herbal drug development, particularly for toxicological and clinical trial studies. This type of approach has been used successfully by the Tropical Diseases Research Programme of the World Health Organization.

The last change which will be discussed is the need for development of clinical pharmacology and the training of clinical pharmacologists, particularly in the developing countries where clinical trials of medicinal plants will have to be undertaken. In the Western countries there are many clinical pharmacologists and several centres for research in this field. None of these centres is interested primarily in medicinal plants or carrying out research in this field. There are very few centres of clinical pharmacology in the third world and even of these, only a handful are interested in herbal medicines. The need for this development becomes more relevant because the emphasis on research of medicinal plants is shifting away from laboratory research to clinical research for plants already in use.

Chinese scientists and clinical investigators have all along stressed the importance of early clinical evaluation of plants and have followed this approach. The traditional approach in India has been to carry out extensive experimental pharmacological and toxicological work before carrying out clinical evaluation. There is now a change in the Indian situation. Plants which are in use today are now being clinically assessed after limited animal toxicology, an approach first suggested by the author in 1980 at the First

World Congress of Clinical Pharmacology in London. The Indian Council of Medical Research has again started supporting clinical evaluation of selected plants for selected conditions. In fact, they are actively developing and coordinating such a programme in several multicentred clinical trials. The conditions selected by the Council are viral hepatitis, diabetes, bronchial asthma, anal fistula, urolithiasis and filaria. Japan has also recently entered the field of research in Kampo medicines, and this will certainly be a gain generally for research in this field.

Will the shift in emphasis from animal pharmacology to clinical evaluation be more successful in developing drugs from medicinal plants? While this would appear to be so, yet there are several obstacles to be overcome. The paucity of clinical pharmacologists interested in medicinal plants and the painfully slow development of clinical pharmacology in the third world has already been discussed. Clinical evaluation is perhaps more difficult than experimental pharmacological studies because one cannot control conditions in patients as one can in animals. A methodology needs to be developed for herbal clinical trial studies, a subject discussed at length elsewhere. It will be optimistic to expect quick answers by changing the emphasis to clinical evaluation.

While a few carefully selected plants could immediately be evaluated for clinical effect, much more effort should be made to develop the infrastructure which is essential for carrying out such studies - developing centres of clinical pharmacology, training doctors in clinical pharmacology of herbal medicines and developing a new methodology for pharmacokinetic, pharmacodynamic and clinical evaluation studies of medicinal plants. If this is done, and adequate pharmaceutical and other resources are allocated to this field, and if a group of imaginative and innovative investigators are induced to enter this field of research, then there certainly will be a new, much-needed thrust forward in research in medicinal plants.

Chapter 4
CLINICAL EVALUATION

THE ultimate demonstration of therapeutic effect of any plant can only be obtained after undertaking properly-designed clinical trials. Chinese scientists have developed a system for rapid clinical evaluation of a plant after obtaining a lead. This has enabled them to carry out a large number of clinical trials even under difficult conditions. For a long time, the concept of use of placebos was not acceptable to the Chinese authorities as it was considered a form of deceit on patients. When the author visited Beijing in 1981, this had changed and active placebo groups were acceptable – the meaning of placebo had then changed from "I deceive" to "I please" in the translation of his lectures. These constraints made it difficult to assess clearly the results of the clinical trials carried out and this problem still persists. Indian scientists and clinical investigators, on the other hand, have been very slow in carrying out clinical trials after obtaining leads in their early pharmacological screening. The pharmacologists would continue to work for a long time on the effect of different extract on different pharmacological systems and the chemists would continue to try and isolate the active principle. It was believed by the Indian scientists, trained as they were in the Western mould of thinking, that clinical evaluation could only be undertaken after exhaustive pharmacological studies, after toxicology – acute and sub-acute – and naturally after obtaining the approval of the appropriate ethical committees. This meant that very few of the leads obtained in the laboratories were actually followed up clinically as it is not easy for an isolated investigator to carry out the acute and sub-acute toxicological studies which would be needed by the ethical committee. It is interesting that this same approach was adopted irrespective of whether the substances being sought to be tested was a recently-synthesized chemical compound, a plant never before used or a plant in widespread use by the local population. Investigators working in Ayurvedic and Unani hospitals and research centres did carry out some clinical trials but they were hampered by the lack of an

appropriate methodology and understanding of the clinical trial methodology as well as general naivety about this difficult type of research. It was to help these investigators that the Department of Pharmacology of the Post-graduate Institute of Medical Education and Research, Chandigarh, organized short courses in clinical pharmacology, concentrating on clinical trial methodology, between 1977 and 1981, which were attended by practitioners of traditional systems of medicine.

The situation, fortunately, has changed somewhat in the last fifteen years but there is still a long way to go. It has now been accepted by several groups that pre-clinical toxicological tests needed for a plant or plant substance actually being used by the people need not be as prolonged and as exhaustive as is necessary for a new synthetic compound or a plant never used before. This had never been a constraint in China but now other drug regulatory authorities are willing to consider requests for clinical trials of herbal remedies after limited toxicological studies. The Swedish Drug Regulatory authorities allowed a clinical trial of zaopatle, the effective agent of the Mexican plant, *Montanoa tomentosa*, used by Mexicans for fertility control, after very limited toxicity studies in animals. The Spanish monk, Fray Bernardino de Sahagun, first described the use of this plant in the form of a tea in 1575. The clinical trial on possible luteolytic effect of the decoction of the zaopatle plant was carried out in Sweden after the following toxicological studies:

- Thirty rats were administered the decoction at three doses for four weeks,
- Four female monkeys were administered the decoction once daily for 30 days, and
- Four adult dogs were given the decoction for twelve weeks.

The usual toxicology profile after administration of the substance was studied in these three species.

Another encouraging example has been the attitude of the Indian Council of Medical Research. The Council is willing to consider allowing, and indeed will be willing to carry out, clinical trials of herbal medicines already in widespread use after limited animal toxicological studies. The Chandigarh group has proposed a modified, six-week toxicological study profile on two species of animals for plants in widespread use in humans. This too has been generally accepted in India, which had earlier been very slow to move from a lead in animal studies to clinical evaluation. It is hoped that things will now move faster. There appears to be a need for a research development funding organization to look at the leads obtained, select those which need further clinical study and then fund such studies. This would lead to drug

development. Otherwise, it will be difficult to see where the funds needed for toxicological studies and clinical evaluation would come from - in the absence of pharmaceutical interest in this field.

This may be the time to look at the traditional approach towards evaluating plants with possible therapeutic effect and compare it with the approach first suggested by the author and his group, at the first World Congress of Clinical Pharmacology and Therapeutics, held in London in 1980, and followed up in several publications. The traditional approach consists of the following ten steps:

- Identification of the plant reportedly in use
- Collection of the plant
- Transport of the plant to the research laboratory
- Storage
- Preparation of extracts for testing
- Administration of the extracts to animal models
- Identification of the active or more active extract
- Further fractionization of the active extract
- Identification of the active principle, chemical structure
- Synthesis of the active substance.

In the alternative or complementing model, these would be replaced by the following steps:

- Toxicity testing of the plant in two species of animals for acute and sub-acute toxicity.
- A modified, shorter toxicity testing if the plant has already been used in man or is in such use now.
- Administration of the total extract or combination of plants, if used, in exactly the same way as it is prepared and used by the population.

The essential differences between this approach and the traditional approach are that in this suggested scheme:

- there is no testing for efficacy carried out on animal models, but only in man;
- human studies are initiated after modified, shortened toxicological studies have demonstrated that the substance is not toxic in animals;
- the duration of the toxicity studies has been decreased to six weeks for plants being used by man, and

- the plant is administered to human subjects in exactly the same manner as is being used in traditional medicine.

The advantages of this model are that it takes into account the concepts of traditional and folklore medicine and avoids some of the pitfalls in the traditional type of screening such as losing the active principle by extraction and fractionation or using an inappropriate animal model. It is, of course, incumbent that approval of the ethical committees involved be obtained before undertaking these clinical trials after limited animal toxicological studies. In Chandigarh, two plants reported to possess anti-fertility properties have already been tested according to this modified approach and the methodology established appears to be working - one of the plants, although being used by people, was dropped because of toxicity findings in animals.

Now that the issue of "when" clinical trials with plants should be initiated has been discussed, it is important to discuss two other related important issues:

- "Who" should carry out the clinical trial?
- "Where" should the clinical trial be carried out?

Since these two issues are necessarily related, these will be dealt with at the same time. Again, several approaches have been tried and it will be useful to learn from the experience gained so that future clinical evaluation will be planned in the most appropriate way. None of the approaches described before have been very successful and any approach in this field will need to be tempered by local conditions.

The first approach is for a pharmacologist, clinical pharmacologist or clinician to be the leader of the team and to carry out the clinical trial in the setting of a modern hospital. While planning the trial, he would closely consult practitioners of traditional systems of medicine but once the trial has been planned, it would be his responsibility to conduct the trial according to a scientific clinical pharmacological methodology. In the planning stages, he needs to be flexible. For example, if the plant extract is brewed in a copper vessel with some black pepper, then that is the way the preparation should be prepared before administering the substance to the subjects.

The second approach is a slight modification of the first. In this approach, the chief investigator will have in his team another group of specialists in the traditional system of medicine. They would help in the planning and conduct of the clinical trial.

Both these approaches have been tried in India and China and both have their limitations. The first approach is being followed at the Postgraduate

Institute of Medical Education and Research, Chandigarh, and the All India Institute of Medical Sciences, New Delhi, in India and at other centres. The difficulty with this approach is that since traditional practitioners – specialists in Ayurvedic or the Unani systems of medicine – are excluded from the actual conduct of the trial, the results of the trial are not really acceptable to them. If we want the results to be accepted by them and action to be taken by them regarding further use or non-use of the herbal medicines, then these persons should be associated with the actual trial. If the purpose of the clinical trial is to determine whether a substance is effective or not, then the first approach works. However, the results of such a trial will influence only the modern specialist – whether to discard the herbal medicine or to study it further. This purpose will be fulfilled but traditional medicine practitioners will continue to use the medicine irrespective of what the results are.

The second approach – to conduct the trial but have in the team of the chief investigator Ayurvedic physicians and specialists in traditional medicine – was adopted very early in this field by the group in Baroda. Special beds were provided for clinical evaluation of traditional medicine and the Professor of Pharmacology who was in charge of the trials, had a team of Ayurvedic physicians in his team. Again, this approach had only limited success and has not been followed up at other centres. There is some reluctance on the part of senior Ayurvedic physicians to form only part of a team led by a specialist of the modern system of medicine. The best would not be attracted. Further, problems in communication, different concepts, and differing meanings to the same phenomenon could make this difficult and lead to ruffled feelings.

A third approach is the one attempted by the Indian Council of Medical Research in their Composite Indigenous Medicine Project. The approach was that the testing would be carried out in the setting of a modern hospital but that the trial will be conducted jointly by a specialist of the modern system of medicine and a specialist of the traditional system of medicine – these would both be equals. This approach too suffered from the problems referred to in the last paragraph.

There was some success in this approach but this was limited and this approach has now been dropped. All the three approaches for clinical evaluation of plants described above have the ingredients of success but have not been successful. Let us now look at the approaches where clinical evaluation is carried out – not in the setting of the hospital or institute of the modern system of medicine but at the institutes or clinics of the traditional systems of medicine.

The most common approach is that the clinicians and clinical investigators at the institutes carry out their own clinical trials and present such results. In

China, such institutes have specialists who are trained in the modern system of medicine and these investigators also help in planning and conducting these trials. Being part of the institute, these investigators are not looked upon as outsiders with a background of a different type of medicine. The problem really is one of expertise in clinical trial methodology which is lacking but which is being developed fast in China at the Institute of Modern Systems of Medicine.

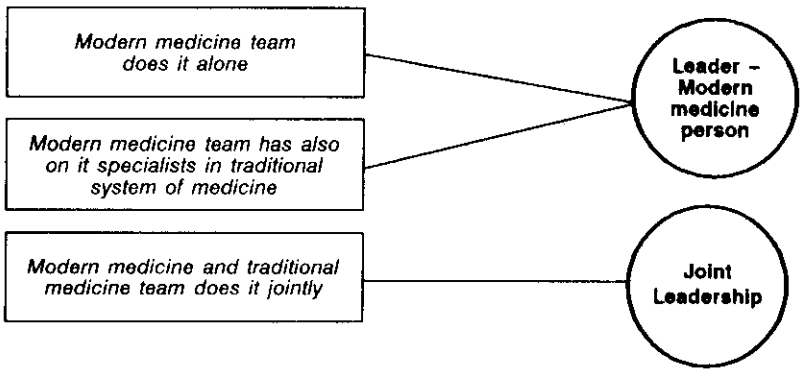
In India, there are three approaches to clinical evaluation of plants in the setting of a traditional medicine institute. This could be carried out entirely by them after developing, if they so desire, a protocol together with a clinical specialist in allopathy or with a pharmacologist or clinical pharmacologist. There are two difficulties inherent in this approach. The clinical trial may not be carried out in the way it should be – selection of subjects, sample size, randomization, assessment of effect – and thus the quality of the trial will be poor. Secondly, specialists of the modern system of medicine will not accept the results of the trials since they have not been associated with the conduct of the trial. They will not agree to use traditional medicine for their patients or even carry out a further trial because they will probably not accept the results. This has been seen time and time again.

The second approach is to have a pharmacologist or clinical pharmacologist in the team of the Ayurvedic or traditional medicine specialist. This helps to some small extent but the acceptance of the results of such trials conducted primarily by a specialist in the Ayurvedic or Unani system of medicine will again not be accepted by the majority of clinicians at medical colleges and medical institutes. The third approach has been a little more successful in those few instances where clinical investigators of the modern system and the system of traditional medicine have trust and respect for each other and for each other's system of medicine and agree to work together and plan and conduct a clinical trial together. If the clinical investigator of the modern system of medicine is a person of stature and reputation, then the results obtained and published by him and his traditional medicine colleague will be accepted by the "modern medicine" community who will then be willing to evaluate the herbal medicine further or even be agreeable to use it. This approach cannot be universally used because in the whole of India, there are perhaps not more than 4-6 outstanding clinicians – leaders in their own field – who would be willing to take a few years off and go and work at an institute such as, for example, the Poddar College of Traditional Medicine, where this approach has been successfully tried with the head of clinical medicine there. Again, there are not more than 3-4 heads of such institutions which would welcome such an association and invite a specialist

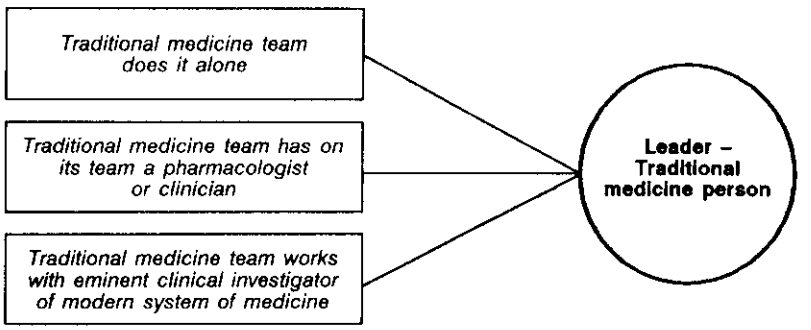
in the modern system of medicine to come and work there. This is a highly personalized approach and has worked because the persons concerned have agreed to work together. Whether this type of approach could be established on an ongoing basis or whether this approach can be widely extended to other colleges and centres of the traditional system of medicine remains to be seen, but is doubtful. A variant of this approach is for the specialist in the Western system of medicine to do the investigations and make the diagnosis and then hand over the patient to the specialists in the traditional system of medicine for treatment. The results of the therapy will be assessed from time to time by the specialist who made the diagnosis. This is the approach being tried out in Kuwait.

To summarize therefore, there are six approaches which have been tried for clinical evaluation of herbal medicines. These are shown in the figure below.

At Modern Medicine Hospital



At Traditional Medicine Setting



Before closing this part of the discussion, it is important to reflect as to why clinical trials of herbal remedies should be carried out at all; who wants these trials to be undertaken. Answers to these important and relevant questions will help to determine where the trial should be carried out and who should carry it out. This will be different from plant to plant and from country to country and that is why no universal guideline on this issue can be laid down.

A clinical trial of a plant may be undertaken in an endeavour to discover a new drug. This will be of interest to pharmaceutical houses who are experts at discovering new drugs, to investigators who have carried out the earlier work, and perhaps to national research authorities in the country where the proposed new drug will have a public health impact, such as development of a new contraceptive in India or a new antimalarial drug in China.

A clinical trial may be planned by a specialist in the traditional system of medicine in an endeavour to demonstrate efficacy, by modern methods, of an age-old remedy. This, however, will be rare, as most specialists in traditional medicine are convinced that their remedies work and that there is no need for further clinical trials. This attitude is found more in India than in China where traditional medicine institutes carry out a lot of work – more on how a herbal remedy works than on whether it works – but such studies also demonstrate the efficacy or the lack of efficacy of the plant.

Finally, research workers of the allopathic system of medicine may well want to carry out clinical trials of herbal remedies to find out whether some of these herbal remedies could be introduced into modern therapeutics. There is, after all, the historical background that about 25 per cent of the medicines being used today are of herbal origin. The interest here is that of the modern specialist or a national council such as the Indian Council of Medical Research. This group will then need to plan these particular trials in such a way that the results will help in the introduction of these herbal remedies in modern therapeutics. Generally, investigators in allopathy are interested in studying plants reported to have therapeutic effect on chronic diseases such as bronchial asthma, rheumatoid and osteoarthritis and liver disease.

The herbal remedies that are being used and could be used further in primary health care will be discussed in more detail in another section. It is, however, quite evident that it is just not possible to carry out clinical evaluation of every plant used at the primary health care level to document its efficacy and safety.

The development of clinical pharmacological expertise in countries with use of herbal remedies has been discussed earlier. Generally, development of this speciality has been slow, and the development of clinical trial methodology, especially pertaining to medicinal plants, has been extremely limited. It is important that investigators carry out clinical trials planned properly, conducted properly and make certain that the results are analysed properly and that correct interpretations are drawn from the results. This needs widespread training in the existing methodology and development of a new methodology.

The different procedures which are used for clinical evaluation of synthetic drugs are now well established. However, all these procedures cannot be used for clinical evaluation of herbal medicines. It will be interesting to have a look at those procedures which cannot be used – as they are – for clinical trials of medicinal plants. The pre-clinical toxicological studies necessary before clinical evaluation of a medicinal plant have already been discussed earlier. It may not be necessary to carry out, for medicinal plants in widespread clinical use, very exhaustive studies which are essential for synthetic compounds before allowing them to be administered for the first time to man.

When a synthetic compound is administered to man, the investigator knows a bit about the metabolic breakdown of the drug and studies are therefore planned in the human to identify the metabolites after administration of the drug. The situation is quite different when working with medicinal plants. The metabolic pathway of the therapeutic principle is not known before the medicinal plant is administered to the human and the breakdown products of this substance in the body cannot be determined during early studies after administration of the drug. There are therefore several different steps which could be carried out when working with a medicinal plant. Selection of a homogeneous sample and determination of an adequate sample size will not present any difficulty in clinical evaluation of plant medicines. However, it may be difficult to carry out double-blind trials with herbal remedies since it may be very difficult to prepare a placebo of the herbal remedy being tested. One may, therefore, have to be content with a single blind design for herbal remedies.

One of the big differences is the sample which is to be tested. The physiochemical properties of a synthetic drug being tested are well known and any subsequent samples of the compound obtained from the chemist for testing would need to conform to those characteristics. The clinical investigator is therefore certain that he is receiving the same substance for testing even if he is given a second or third batch of the material. Things

are quite different with medicinal plants. Since the physiochemical characteristics of the plant substance being tested have not been characterized, it will be difficult to ensure that the second, or perhaps even the third or the fourth sample of the plant material received for testing contains material with exactly the same physiochemical and pharmacological characteristics as the first sample. This means that, for a successful clinical trial with a medicinal plant, all the material, collected at the same time of the year, from the same location, would need to be made before the clinical trial is undertaken. The material should be used for the total study, and other samples, collected perhaps at a different location, or at a different time of the year, should not be used for this trial. This is very important and would enable one to avoid some of the problems which have been referred to earlier. It also means that studies have to be carried out to demonstrate that the physiochemical and pharmacological properties of the plant do not alter during storage.

Cross-over studies with a wash-out period can be carried out with synthetic drugs because the metabolic pathway and excretory metabolites of the compound are known, as also the half life of the compound, before administration. It is then not difficult with this information to identify a suitable period for the wash-out period. Unfortunately, this cannot be done for medicinal plants as there is no rational way in which the "wash-out" period can be arrived at without knowing the metabolic pathway and half life of the active principle of the plant substance nor the time for excretion of the metabolites. These are some of the differences which need to be kept in mind when planning a clinical trial of a medicinal plant. There are others, such as use of additional plants for the treatment of other conditions during the trial, possible interaction between plants, and the effect of the plant on other systems such as the hepatic, renal or metabolic systems about which the trained investigator in clinical pharmacology may not even be aware of. It will be useful to list these differences for the reader:

- Pharmacokinetics of plant substance not known before administration to man.
- Pre-clinical toxicology requirements may be different.
- Metabolic breakdown products in man and half life in the human not known.
- Cross-over studies not possible and wash-out period cannot be calculated.
- Double-blind studies are difficult as it may be difficult to prepare an identical placebo substance.

- The sample to be used throughout the trial needs to be fully collected before the start of the trial.
- Physiochemical and pharmacological characteristics of the plant substance should be checked during storage to confirm that no deterioration during storage has taken place.
- Effect of plant – plant interaction to be carefully noted and administration of second plant avoided, if possible, during the trial.
- Effect of the plant being tested on other systems needs to be known to interpret results well.

The foregoing discussion relates to a clinical trial when one plant or plant substance is being tested. The differences that will be encountered when a combination of three or four plants is being tested or when a plant or two plants need to be tested in the presence of one or two activating substances, such as honey or black pepper, will be more and the complications greater. That is why it is important not to depend entirely on the clinical trial methodology developed for synthetic compounds but to develop a modified clinical trial methodology which will be appropriate for testing medicinal plants.

Chapter 5
PRIMARY HEALTH CARE

IN the third world, most people go first to a herbalist for the treatment of simple and common conditions. This trend is also becoming evident in some of the developed countries. Interest in the use of plants for therapeutic purposes is growing. A recent visit to Boots at Oxford showed that several preparations are available for use by the public. No prescription is needed for obtaining these medicines. Some of the plants used in these prescriptions include *Tanacetum parthenium* (feverfew), *Marrubium vulgare* (horehound), *Valerian valeriana* (valeriana officinalis), *Menyanthes trifoliata* (bugbean), *Apium graveolens* (celery), primrose and *Articum lapra* (burdock).

Irrespective of what policies governments of countries with a heritage and tradition of herbal remedies have, the use of medicinal plants will always remain one of the main planks for the delivery of primary health care service in these countries. More and more governments have come to recognize this and are trying to improve the traditional system of medicine and to bring it within the purview of the government health services. It is here that problems arise since it is not clear as to what needs to be done. China, which led the way with the creation of the "barefoot doctor", does not need this doctor any more and is stopping this programme. However, China is perhaps one of the few countries where government policies regarding traditional medicine and allopathic medicine are very clear – integration of both systems is the ultimate aim. In contrast, the different systems of traditional medicine in India – Ayurveda, Unani, Homeopathy, Siddha and Naturopathy run parallel to one another and to the allopathic system of medicine. Each has its own teaching institutes and training centres, clinics, health centres, hospitals and teaching hospitals. Integration is not always sought; and even where it is sought to be carried out, not much has been done about it.

One of the questions always asked about the use of traditional medicines and herbal remedies is: "Does it work?" The answer is that this is not known and will not be known till clinical evaluation of these remedies are carried out. It is not possible to carry out all the clinical trials needed to document whether hundreds of plants being used for primary health care are effective or not. At this juncture, it is important to go deeper into this and try to find out why clinical trials should be carried out and who actually wants to know whether these plants are effective or not. Neither traditional medicine practitioners nor patients who have always used traditional medicine are interested to find out whether the herbal remedy acts. The practitioner feels that the plants act and the patient believes that the plant medicine being administered to him works. Neither will be impressed if, after years of research, they are informed that a plant substance used for a thousand years and being used at this moment of time, perhaps, is effective. Both the patient and the traditional medicine practitioner know, and have always believed, that the plant is effective. If, again, after years of research it is shown that a plant or a plant substance is not effective, this will hardly have any effect and both the practitioner and the patient will continue to use the plant. It is, therefore, the allopathic practitioner and perhaps the health administrator who are anxious to know whether the plants used are effective. They are keen to know this because, if the plant is effective, this could be added on to the armamentarium of drugs already available to treat a particular disease.

In this chapter, we are not discussing plants being used, which may be the source of discovery of a new drug. That has been dealt with in the section on research and there are investigators who are all the time seeking a new cure for some of the refractory diseases such as hypertension, liver disease, arthritis and bronchial asthma. Investigators will certainly be interested in assessing plants thought to possess this type of activity so that a new discovery may be made. This can, however, be carried out with very few carefully selected plants as the work involved is time-consuming and expensive. The issue of plants being used in primary health care is quite different. There is hardly a discovery to be made here. There is therefore not much reason for carrying out clinical trials to determine the efficacy of these plants. Combined with the enormous logistics of carrying out clinical trials with herbs used all around the world, one cannot but come to the conclusion that there is no reason to clinically evaluate all these plants. It will be an enormous task with little outcome. The few trained clinical investigators and clinical pharmacologists in the third world could do much more important work than planning and conducting unnecessary clinical trials with hundreds of these plants. They could help in better use of essential synthetic drugs and could

carry out research – clinical research – on one or, at the most, two plants which could lead to the discovery of a new therapeutic agent.

There is, however, much, apart from clinical evaluations, which could be done as regards plants being used in primary health care. One of the first things to do is to prepare a list of herbal remedies or plants which should be used for primary health care in a particular country. Such a list of about thirty-five formulations has been prepared for Myanmar. In another section of this book – the one dealing with selection – two lists of plants have been suggested for use at the primary health care level. One is a list suggested from India while the second is a list prepared by representatives of countries of the Eastern Mediterranean Region of WHO.

Once the list of plants to be used in a particular country has been prepared, it will then be important to take steps to ensure that adequate supplies of these herbs – of good quality – are always available at the primary health centres. This means estimating how much of each of these substances will be required; then calculating how much raw material needs to be imported. Steps then need to be taken to grow whatever is needed in the country and to import the plant substance which would need to be imported. It would also be important to make certain that the crude plant material is of good quality, is unadulterated and can be tested for quality assurance. Finally, steps need to be taken for proper storage of these plant substances and distribution, at regular intervals, to the primary health centres so that the plant medicines will always be available. These are important things to do but by doing this one makes certain that plant medicines will be used more effectively than they are being used at the present time at the primary health care level. It will be much more useful to spend time, money and resources on the above-mentioned activities than in carrying out clinical trials of herbal medicines used at the primary health care level.

There are a few more issues to be discussed. One relates to the type of person who is to prescribe the herbal remedy. Past experience has shown that the patient would like the traditional medicine practitioners whom he knows and in whom he has trust to give him the medicine. The use of a herbal remedy is linked, in his mind, to a particular person giving the medicine and he will not readily accept these from others. He will be just as loth to accept this type of medicine from an allopathic practitioner, even after training in traditional medicine, or from a health assistant or community health worker, even after training, just as a patient going to a modern hospital would be loth to accept allopathic medicines from a traditional medical practitioner trained for six months to a year in modern therapeutics. It was naive, for

example, for the national programme authorities in India to expect that community health workers, after training, would successfully treat patients with herbal remedies. A study conducted by the author and his colleagues quickly demonstrated that while all the allopathic medicines were rapidly used up at the primary health care level, the herbal medicines remained stacked. There was nothing wrong with the medicines but the persons giving the medicines were not acceptable. It would therefore be unwise if countries were to start retraining thousands of health personnel of the allopathic system of medicine in traditional medicine in the hope of using these medicines at the primary health care level. The only exception could perhaps be China but the situation there in this regard will be dealt with later.

It will be preferable to use the traditional medicine practitioners to deliver primary health care through the use of herbal medicines. The number of such practitioners could be increased; their training could be improved; they could be retrained in a programme of continuing education and they could be provided with safe and effective herbal remedies. This approach is much more likely to succeed. It may even be considered whether it may not be advisable to leave these traditional medicine practitioners outside the framework of the national health service. This would depend upon the country but it is very likely that the traditional medicine practitioners would function more effectively outside the system than being in the health system of the country. Experience gained recently in Somalia and some other countries supports this contention.

This leads then to the resources being used for developing training material in the form of manuals and guides for the use of non-traditional medicine practitioners who are being trained to prescribe herbal drugs within the ambit of the health system of the countries. A careful look needs to be made as to whether these really will be useful. It is natural that governments will look first to manpower existing within the health services and hope that with training and buttressed with guides, manuals and other documentation, this same manpower will be able to prescribe traditional medicines. This may be too optimistic.

One thing that will however be most useful and help in more effective and better use of herbal remedies will be the production and widespread dissemination of a herbal formulary. This will be of use both to the traditional medicine practitioners and to persons of the modern system of medicine and allied paraprofessionals of this system. This formulary could, of course, be prepared only after a country has already identified and made a list of the plants that it would like to use at the primary health care level. A representative

group of experts meeting at a WHO Inter-Regional Workshop on The Selection and Use of Traditional Remedies in Primary Health Care in Bangkok in December 1985, in fact, suggested that the formulary should include the following information:

- Name of plant (genus, species, authority and family)
- Plant part used
- Quality requirement (percentage of active principle, if known)
- Botanical characteristics
  - Macroscopic morphological description, including organoleptic tests.
  - Microscopic description
  - *Histological character*
  - Powdered sample character
- Purity (foreign matter, adulterant, other containments)
- Physicochemical analysis
  - Qualitative (including microchemical tests)
  - Quantitative (if major active ingredients are known, analytical procedures [e.g. thin layer chromatography, high pressure liquid chromatography, nuclear magnetic resonance] should be developed to quantify the total and individual constituents). Even if active principles are unknown, one can still obtain characteristic special profiles for the plant material.
- Bioassays
  - *In vitro*
  - *In vivo*
- Pharmacological/biological category for which the herbal product is indicated.
- Posology (dose and directions for use)
- Toxicity/contraindications with appropriate warning information.
- *Packing and storage*
- Proper packaging, storage and shelf life.

The report of the Workshop (TRM/86.1) states that the guidelines were later modified and adopted. One need not agree with all that has been suggested in this particular outline of a herbal formulary and it could perhaps be made shorter and simpler. It could, for example, provide information only on nomenclature, procedures of preparation, dosages, indications, contraindications and adverse reactions which should be looked for. What

is important is to develop a herbal formulary which will certainly help in improved herbal therapeutics. This point has not only been made by participants at this meeting but at two other WHO meetings, held also, interestingly enough, in 1985. The first time that the suggestion was made was in a Meeting on Use of Medicinal Plants at the Primary Health Care Level, held for representatives of countries of the Eastern Mediterranean Region, in Kuwait, in April 1985 (EM/Pharm/107), and the second time at an Inter-Regional Seminar on The Role of Traditional Medicine in Primary Health Care, held in China in October 1985. It is important, therefore, that countries try and produce their own herbal formularies.

The use of medicinal plants at the primary health care level has several advantages and should be encouraged. In many parts of the world, there are no doctors and no allopathic drugs. Very often, there are doctors but the government budget has run out and there are no medicines to distribute. Sometimes allopathic drugs of indeterminate quality of doubtful origin are smuggled across borders and sold in open markets. Many of these substances have no expiry date. It would be better, in these circumstances, to use herbal medicines chosen with care, supplied with a guarantee of quality, prescribed by practitioners in whom the patients have trust. The use of such medicinal plants should be monitored and changes made in the list of traditional medicines at the peripheral health centres based on the ongoing experience. The easy availability of these drugs at all times, the relatively low cost of these medicines and less side-effects associated with the use of these drugs are some of the factors which may eventually lead to the replacement of some of the modern medicines used at the primary health care level by medicinal plants.

The fact that these plants are locally grown and will always be available provides a morale-boosting effect which cannot be appreciated by persons who have never experienced sickness or illness without medicines being available. Countries in South-East Asia will remember the time during the Second World War when medicines from the Western world were not available in countries under Japanese occupation as were drugs from Japan. People in countries, such as Myanmar, had to depend once again on herbal remedies from medicinal plants. This deprivation of modern medicines has left a mark and many persons in these countries would prefer to take herbal remedies which they feel is "their" medicine, grows in their country and which will always be available. Arab oil-producing countries also experienced a boycott of Western modern medicines when action was taken by the Western countries to cut off imports of medicine into these countries. People in these countries

still remember this and wish to have self-sufficiency in the production of essential "Western" drugs and encourage more widespread use of herbal medicines. These will, in fact, be an insurance against such a situation developing again.

The increased use of medicinal plants will probably lead to some financial savings. The cost of herbal medicines may, in fact, in some cases, be more than the cost of allopathic medicines. However, as the quantum of use of these medicinal plants increases, as it is hoped they would, the cost would increase.

While the cost of medicinal plants may or may not be less than that of allopathic medicines, it is generally accepted that side-effects induced by herbal remedies and interactions between herbal remedies will be less than those seen when only allopathic medicines are used. Generally, it is felt that herbal medicines would induce less side-effects. It must, however, be recognized that medicinal plants too induce side-effects. Interaction between medicinal plants has also always been recognized in the ancient Indian, Chinese and other systems of traditional medicine. The reason for the concept of Monarch, Minister, Assistant and Guide medicinal plants in the Chinese system of traditional medicine, was, in fact, a mechanism to avoid interactions between plants leading to undesirable side-effects. No two Monarch plants, for example, would ever be put in the same preparation, nor would too many Ministers be put together. Similarly, plants are divided, in the Tibetan systems of medicine, according to taste. The plants are classified as (a) sweet, (b) sour, (c) salty, (d) bitter, (e) acrid, and (f) stringent. A "sweet" plant, for example, *Glycyrrhiza glabra*, will decrease body heat while a "sour" plant, for example, *Punica gratum*, will promote body heat. In the Tibetan system of medicine, these two plants would never be put in the same prescription indicating that physiological incompatibility had been recognized in the ancient traditional systems of medicine over the last 1500 years.

It has been mentioned earlier that China is perhaps the only country where government policies today are absolutely clear in stating clearly that integration of the traditional and allopathic systems and an unified approach to health care, not only at the primary health care level but at all levels, is their objective. In their endeavour to achieve this objective, several innovative approaches have been carried out. Doctors trained in the allopathic system are encouraged to attend a two-year training course in the Chinese system of traditional medicine, which includes, besides the use of medicinal plants, treatment by moxibustion, acupuncture and massage. Over 4 000 doctors have already taken this course and are, therefore, in a position to treat patients

either with allopathic medicine or with medicines from the traditional system of medicine. Both systems of medicine can run side by side at the same hospital; sometimes doctors from the different systems examine the patient together and decide which system of medicine should be used. If the patient has preference for a particular system of medicine he should be treated with, that wish is respected. In addition, practitioners of the Chinese traditional system of medicine are encouraged to hand down to the next generation some of the knowledge they have and the experience they have gained in traditional medicine. They are encouraged to take on apprentices and to run small classes, if necessary. To further propagate the scientific use of traditional medicines, the College of Traditional Medicine in Liaoning Province in North-East China has offered, since 1977, a correspondence course in traditional medicine for rural doctors, basic health workers and other paraprofessional health care workers. The training lasts 2-3 years. Students work under part-time or full-time teachers at the field stations.

China therefore provides us the only example of integration of the two systems working side by side at the primary health care level. In effect, the country has three types of doctors: allopathic doctors, doctors trained in the traditional system of Chinese medicine and doctors trained in both the systems. There are over 1.25 million rural doctors in China and over 1.9 million health aides and rural midwives. Gradually, more and more of these are being trained in the traditional system of medicine. A time may come when most of these people will be able to use medicines from both systems of medicine in their work. The Chinese experience will be looked at carefully in the years to come, more particularly since their very successful programme in the use of barefoot doctors has now been curtailed.

In most developing countries where integration has not been attempted or has not been as successful as in China, it would be enough to:

- prepare lists of herbal remedies to be used in that district or region;
- arrange for regular supply of such remedies of good quality either through local or regional herbal gardens or a centralized supply;
- train traditional medical practitioners, if necessary, and the community to use these remedies better, and
- develop herbal formularies.

These few steps will do much to spread the use of medicinal plants at the primary health care level and complement the existing facilities in the modern system of medicine. Persons not receiving medical care will receive

medicines and the widespread use of these traditional medicines will reduce the cost of the medicines. The list of such plants should be carefully selected and reviewed from time to time. Publications containing description of plant medicines being used as household remedies in both the Unani and the Ayurvedic systems of medicines have been brought out by the Government of India while WHO has issued publications on medicinal plants being used in some countries. These are steps in the right direction but even in these publications, there is no selection and recommendation. This is what is needed. There is no need to carry out clinical trials for efficacy and safety with every plant used all over the world at the primary health care level. Not only is this not necessary but it is not possible.

The fact that medicinal plants may have to be administered as aqueous or alcoholic extract to exert their full activity is no constraint for their use for primary health care. Extracts can be put through the process of freeze-drying and granules supplied to the primary health centres. Granules containing herbal teas, for example, are available and distributed throughout the United Kingdom and Europe in this form. If an agueous extract has to be used, the granules have just to be dissolved in water and used. If an alcoholic extract has to be used, one of the persons at the primary health centre can easily be trained to prepare an alcoholic extract of the granules just before distribution.

Chapter 6
STANDARDIZATION

WHEN a medicine is administered to a patient, the doctor who prescribes the medicine needs to be assured that the medicine contains the correct amount of the right substances as only then would the medicine induce its therapeutic effect. This is assured both to the doctors and the patient by the pharmaceutical company producing the medicine. In the laboratories of the pharmaceutical house, the medicine – or batches of the same – have been tested for quality and quantity and the drug is released for use only if the quality control laboratories of the pharmaceutical house approve the batch in question. Overseeing the situation nationally are national drug control laboratories run by government scientists who also monitor the quality of the drugs being released by carrying out random checks to ensure that the results conform to the standards laid down by both the pharmaceutical house and the national drug regulatory authority at a time when the pharmaceutical house requests for the release of a particular drug in the market. This is known as standardization – a system to ensure that every packet of medicine that is being sold has the correct substance in the correct amount and will induce its therapeutic effect.

This system has worked well in developed countries and reasonably well in countries in the third world, particularly if the country has a strong drug regulatory agency with its own laboratories. However, the system has been developed for synthetic medicines and it has not been difficult to "fingerprint" the synthetic medicines and lay down standards. It is much more difficult to ensure that this system works in regard to herbal medicines.

It is very important that a system of standardization is established for every plant medicine in the market because the scope for variation in different batches of medicine is enormous. Plant material, as has already been mentioned earlier, may vary in its alkaloid content and therefore in its

therapeutic effect according to different places of collection, with different times in a year for collection, with collection at the same time and place but in different years, and with different environmental factors surrounding the cultivation of a particular medicinal plant. Adding to this variability is the fact that in herbal medicine several plants may be used together in the same preparation. This means that there should be a quality control test for the entire preparation to ensure quality of the preparation.

As long as herbal medicines were grown locally, perhaps even in a kitchen garden and used fresh, for example, as a tea, whenever needed, it may not have been necessary to carry out extensive procedures of standardization. During the author's first visit to China in 1981, the Chinese scientists could not always fully comprehend the scope of standardization when he raised this topic since they were largely using freshly-prepared herbal medicines. However, the position changed and by the time of his next visit in 1985, most scientists involved with the development of herbal medicines were very concerned about standardization. Herbal medicines were now being prepared in factories and pharmaceutical houses and packed for use all over the country and also for export. Quality control had therefore to be carried out with their products and this could only be carried out if standards had been laid down to ensure quality. These standards had to be developed for different plants and for the final products and the whole issue of standardization of herbal remedies and medicinal plants came to the fore.

Before considering this issue in more detail, two things should be kept in mind. If plants are used fresh, after brewing as a tea or as a juice, it is probably not necessary to carry out tests for quality control. However, the moment plant substances are prepared for storage and subsequent use, it is essential to carry out tests to check that the standards are being maintained.

The second point to remember is that when plants are used fresh – and perhaps cultivated in the kitchen garden or village garden – these lead to cheap remedies. However, if tests for standardization of plant preparations has to be carried out and if standards are maintained, this requires the use of some sophisticated equipment and the time of suitably-trained technicians and supervisors. This inevitably means that this cost will be added on to the price of the herbal medicine which does not remain a cheap medicine any more. That is why it has often been stated that herbal medicines are, in fact, not cheap. This depends on the way herbal medicine is used. With elaborate quality control tests needed for four to five ingredients and the product, a herbal medicine may indeed be more expensive than a synthetic drug for the same purpose.

It is generally felt that standards can only be established for an isolated compound. Interest in developing extracts for use – both at the primary health care level and more widely – is therefore tempered by a feeling that these extracts cannot be standardized and therefore the extracts are not a marketable commodity. Development of therapeutic substances concentrates on isolated compounds and those plants in which an isolated compound cannot be obtained are not followed up. It has been stated earlier that biological activity present in some extracts will be present when the plant is in an extract form only.

The full pharmacological effect will be decreased or even disappear if further extraction and fractionation is carried out. If specialists in the modern system of medicine want to use some of the medicinal plants in use today e.g. an extract of *Momordica charantia* for diabetes mellitus, they will need to consider working with extracts. It should be clearly stated that extracts can be standardized and the lack of a standardization methodology today should not be a reason for not working with extracts. There may be other reasons for not working with extracts but the lack of standardization is not one of them. If the method of production of the extract is properly standardized and if there is an appropriate chemical assay method developed, there is no reason why standards cannot be developed for an extract or a fraction. Further, this will be augmented by a bioassay method which would certainly be available. Once this reservation in thinking is overcome, a wide range of medicinal plants becomes available for investigation, for isolating maximum activity in an extract and for using the extract.

Another apparent constraint in standardization appears to be a preoccupation of chemists and pharmacologists with a medicinal plant having only one active principle which needs to be standardized. Again, if modern medicine is to take advantage of medicinal plants used in the traditional systems of medicine, then one has to accept that, in many instances, the pharmacological and therapeutic activity will not be residing in one active substance but may, in fact, be present in a combination of a few active substances. As far as standardization is concerned, this again need not be an insurmountable barrier because all the active substances could be identified and standards set for each of these.

Once scientists in the field of medicinal plants research accept these two "facts of life" – that standards have to be set for extracts and that standards may have to be set for several active substances in a plant – and once they work towards these goals, there will certainly be advances in the field. Such advances have been lacking in the last two decades. Participants at two recent international meetings organized by WHO have clearly pointed out the problems

relating to standardization of herbal medicines and the tremendous need for urgent immediate work in this field. The first was an Interregional Meeting on Standardization and Use of Medicinal Plants, held in Tianjin, China, in November 1980, while the second was a Conference on Research in Traditional Medicine, held in Tokyo in March 1986. This meeting identified three areas of priority for research, and research on standardization was one of these. Standardization of a plant produce entails standardization of the raw material, standardization of the method of production and quality control of the final product.

Identification of the actual plant is not easy. Sometimes two plants are known by the same local name. When the plant is being collected, it is very possible that another plant is being collected at the same time and this will be mixed up with the plant which actually has the activity. One example of this is manifest when one collects the plant, *Boerhaavia diffusa*, which is used widely as a "quality of life enhancer" in the traditional systems of medicine. However, both *Boerhaavia diffusa* and the plant, *Trianthema portulacastrum*, are known as "Punarva", and so both plants may be collected at the same time.

A second area of concern is that plant collectors may substitute cheaper plant material that looks the same, for the actual plant material which has the therapeutic effect. In this case, it is not a case of inadvertent mistaking a non-medicinal plant for a medicinal plant, as described in the last paragraph, but one of adulteration and cheating. One example which is very well known concerns the bark of *Caesalpina sappen*. When this substance is collected, bark from other plants such as *Pterocarpus*, *Gluta Travancorea* and *Toona cilita* are substituted for the bark of *Caesalpina sappen*. Other examples with commonly-used medicinal plants in India are substitution of the bark of *Saraca indica* by the bark of Trema orientalis and substitution of the plant, *Halarrhena antidysentarica*, by the plant *Wrightia tinctoria*. It is very important, therefore, when laying down standards for a herbal product – either for experimental research, clinical evaluation or widespread commercial use – to lay down clear-cut standard nomenclatures and clear-cut criteria to actually "finger print" that the substance being used is actually the substance which should be used. Once it has become clear that the substance being used is the substance meant to be used, the first hurdle in standardization of the preparation is overcome. Every crude ingredient going into the herbal preparation must be clearly identified.

The next step is to standardize the method of production. This could be the method, as it usually is today, of isolating the compound which is to be used or the method for preparing the extract which is to be used. The steps leading up to this should be clearly described and the end points defined.

Finally, procedures have to be developed for laying down standards for the final product – if it is a single substance or for the final formulation – if it is a mixture of substances. These standards would attest to the quality of the final product and would comprise both physiochemical methods and biological tests of efficiency. If mixtures or extracts are to be used as the final product, then methods for standardization of the mixtures or extracts should be developed. These standards should be strictly adhered to.

It has been stated very often that the lack of standardization of herbal remedies and plant medicines is holding back the use of medicinal plants in the modern system of medicine. It has also been said that practitioners of the modern system of medicine cannot have confidence in the use of herbal medicines and do not want to use such medicines because they are not certain that the substance being used is what it is supposed to contain. This sentiment is not confined to practitioners of the modern systems of medicine. At the III International Congress of Traditional Asian Medicine, held in Bombay from 4 to 9 January 1990, similar views were expressed by a large number of participants who did not belong to the allopathic medical profession. Botanists brought out the difficulty in the identification of Artemesias as the herbs and shrubs belong to at least ten species of Artemesia. A group of Ayurvedic research workers stressed the importance of developing good methods for standardizing crude extracts, decoctions and compound formulations which consist of different ingredients. It was clearly stated that the technology currently available is not able to develop suitable quality control criteria for mixtures and compound preparations. Research, therefore, should be carried out to develop the methodology needed for the standardization of such preparations as otherwise these could never be used either for primary health care or more widely.

Another investigator suggested that extensive work be put into the methodology of standardization keeping in view the very intricate and complicated system being dealt with. He pointed out that the biological activity of a plant depended not only on the use of the proper plant and its contents but also on the presence of the required quality and nature of secondary metabolites in the raw drug. The availability of these secondary metabolites depended on environmental and other factors such as time and season for collection, stage of plant growth, storage, drying procedure and geographical variation. Unless clear-cut standards are laid down for the evaluation of the final product, these factors could certainly modify and affect the efficiency of the product and lead to failures in therapy. Still another investigator stressed the need to develop methods for rapidly determining whether the plants being

collected were authentic and whether the quality of the material used was up to the standard.

There appears, therefore, to be a general consensus that the lack of standardization constitutes a major constraint to the development and use of medicinal plants; that this need is felt by practitioners of both the modern and the traditional systems of medicine and that the area which needs attention is that for developing a methodology. It is very interesting to note that researchers and practitioners of the traditional systems of medicine do not have any reservation about the use of modern technology for developing methods for standardization. In fact, these workers have often stressed not only that all modern methods should be used and that these methods are not always adequate and that more sophisticated and more advanced tests should be devised.

Generally, the tests for standardization of plant medicines in use today are macroscopic, microscopic, physicochemical and biological. It is not the place to deal critically and exhaustively with these tests nor is the author competent to do so. The list of tests generally used is given below.

- Macroscopic examination
- Microscopic examination, e.g.

  anatomical structure
  detailed study of fragments

- Physicochemical testing, e.g.

  boiling point
  freezing point
  absorption coefficient
  loss on drying
  ash value
  refractory index
  optical ratio
  water/alcohol soluble solid
  spectroscopic analysis
  thin layer chromatography – R.F. value
  gas liquid chromatography

- Biological testing where appropriate, e.g.

  digitalis bioassay

If a herbal remedy or a plant medicine is sought to be prepared for clinical trial or for wide use, it is essential that it passes the tests appropriate for the particular plant described above. Safety and efficiency need to be evaluated and documented. Only then will practitioners have confidence in the herbal medicines they use. Even these test methods are not adequate. More tests have to be developed to cope with the enormous variability that may be encountered. However time-consuming or expensive this area of work may be, this has to be undertaken if we are interested in utilizing the heritage of medicinal plants available for use. If we are not prepared to expend the time, resources and superior calibre manpower needed, then we will never be able to develop more medicines from plants. The great effort and crusade for saving the rain forests – one reason for which is that these forests contain plants which would be the source of medicines in the future – would have been in vain and would remain a hollow sentiment. The best brains and sizable resources need to be put, not only in the area of standardization but also in allied areas such as pharmacokinetic studies with plants, clinical evaluation methodology, development of toxicology models and development of clinical pharmacology in the third world where these plants are being used. Only then could we hope to use properly the herbal remedies we have or discover new medicines from plants in the coming century.

Chapter 7
REGULATION

ALL countries where medicinal plants and traditional medicines are used are aware of the need for regulating the use of these medicinal substances. Some countries where the traditional systems continue to be used as a form of medicine have a heritage in the use of these substances long before the modern system was used. India and China are examples. In other countries, the main system of medicine is the well-developed modern system of medicine but traditional folk medicine, without teaching or textbooks, has always been, to some extent, practised in the countries. Examples are the United Kingdom and Germany. Finally, there are countries where herbal remedies were not used, to any appreciable extent, in the past and the system of medicine always in use has been the modern allopathic system of medicine. However, there is a need for these countries also to regulate the use of medicinal plants because of migrant population who would like to continue to use the herbal remedies they have been used to and because there is a growing interest in herbs as medicines in the population of these countries. Examples are Canada and Australia.

In the next few pages, a very brief account will be given about how herbal remedies are sought to be regulated in countries falling into these three categories. The practice followed in India, China, United Kingdom, Canada, Australia and the United States of America are briefly described. Regulations change from time to time but every effort has been made to describe accurately the situation prevailing in these countries. Following these descriptions, an attempt has been made to compare these different regulatory practices.

Finally, the outcome of a meeting specially organized by the Eastern Mediterranean Regional Office in Alexandria to develop broad guidelines for regulating the use of herbal medicines will be described. This meeting was held in Kuwait in April 1986 and the proposed draft Act which could be used by countries all over the world using medicinal plants for therapy has already

been published as an Eastern Mediterranean Regional Office document – WHO – EM/PHARM/119-E. Unfortunately, this important document has not been given the attention it deserves. With the permission of the Regional Director of the Eastern Mediterranean Regional Office of WHO, a "Note for the Guidance of Persons Applying for the Regulation of Herbal Remedies" has been included in this book as Annex.

India

Medicinal plants are used for therapeutic purposes in India in several ways. As in other countries with well-developed systems of modern medicine, there are many drugs used which have been derived from plants e.g. digitalis, morphine, atropine, cinchona and vinblastine. These are reviewed as any other synthetic medicine and if a new medicine of this type has to be introduced into the market, an application for this purpose needs to be supported with full pharmacological, toxicological, and later pharmacokinetic and early clinical trials data.

Several plants are used either alone or in combination in the traditional systems of medicine being practised in India i.e. Ayurveda, Siddha and Unani. The regulations state that if these medicines are prepared in exactly the same way as it has been recommended in the ancient Indian medical books and texts and if it is preserved in the same way as has been described it should, then these medicines do not require approval or registration. They could be freely prepared and freely distributed. The manufacturer of these substances is responsible for the quality of the plant medicine and, as far as the author can gather, no checks for quality are made on a random basis by any governmental organization.

If, however, an old medicinal plant, described in the ancient literature and medicinal texts, is sought to be prepared in a different manner from that described in the literature, then, even if this difference consists of a few different chemical steps or a new ingredient or has one ingredient less, this medicine is considered as a new medicine for use. This will be treated as any new drug before it is released in the market for use either in the traditional system of medicine or the modern system of medicine. Application for such use will have to be supported by full data, as has already been described.

There is nothing in the regulation to indicate that the requirements before the release of such "new" but old herbal medicines are in any way less demanding than what these are for synthetic medicines although, as always, special dispensation from particular requirements will necessarily have to be asked for and will be agreed upon, if justified. Before *Commifera mukul* could

undergo clinical evaluation in its new composition and form, it was considered for review as a new substance although the plant itself has been used for 1500 years. It was also being sought to be used for a new condition – hyperlipidemia – which of course, was not described in the old texts. It was described earlier as being useful for metabolic disorders related to obesity.

Finally, there are hundreds of plant medicines being locally prepared by herbalists and given to their patients. There are large suppliers of raw materials of these herbs and crude substances who collect these in different parts of India – mainly in the Himalayan regions of the state of Uttar Pradesh – who transport these to larger centres and sell these to herbalists and traditional practitioners. Like their counterparts in other countries, such as Sri Lanka, Nepal, Myanmar and Thailand, traditional medical practitioners and traditional medicine manufacturers have developed a fine sense of quality control. By smell, taste, feel and look, they can know whether the plant, plant substance or crude plant material is of the requisite quality. No chemical or physicochemical tests on the part of these persons are required to know quite clearly which are acceptable substances and which are not. They can, of course, make out if the actual plant material has been substituted by another plant substance which does not have the required pharmacological or therapeutic effect. These are not accepted.

The Government does not exercise any regulatory control over the use of such "home-made" remedies which are used by a large segment of the Indian population.

China

In China, it is quite legal to sell medicinal plants and herbs in the free market, both in rural and urban areas. This would account for a large volume of the use of herbal remedies in the country. However, if a new medicinal plant product or a crude drug is to be imported from aborad to be sold in the Chinese market, then the approval of the provincial department of public health is required. The Pharmacopoeia of the Peoples's Republic of China has got a section on "Standard for Processing of Chinese Material Medica". This new plant substance or crude material being imported will have to be assessed according to the standards described in the Pharmacopoeia and approval either given or not given. The origin of the crude drug or the herbal product must always be clearly marked.

If Chinese herbal medicines are produced in factories either for export or for local use in other parts of the country, these have to undergo quality

control tests before being released. Each factory has its own quality control unit which checks on the quality of different samples of the product. An attempt is being made to ensure that the quality of Chinese traditional medicine produced in China is of a high standard. An attempt is being made – for the first time, as far as the author is aware of – keeping in mind the various variability factors when choosing the standard substance against which all preparations will need to be tested. These factors, such as climate, soil, time of collection and place of collection are important both for the sample, which will be the standard sample and other samples, which represent the herbal product about to be released.

Another set of rigid criteria has been laid down for assessing patented traditional Chinese medicines. While applying for permission to market these medicines, the manufacturer will need to list the main ingredient and the other ingredients. The reviewing authorities will review this compound according to the concepts and practice of Chinese traditional medicine and will also observe closely whether there may be incompatibility between the different ingredients. Only after assuring themselves that the product conforms to the Chinese traditional system of medicine, that it is safe and that the ingredients are not incompatible with each other will the patent medicine be allowed to be released into the market. The determiniation of efficacy of the product for the condition for which it is being sought to be used is not a criterion, as can be seen by the many patent medicines available in the Chinese market.

It is interesting that the review and assessement is carried out largely by persons trained in the traditional Chinese system of medicine. This is not always so in other countries. In the last 40 years, the production of Chinese herbal medicines, both for use in the country and for export, has increased tremendously. Over 250 000 persons are now engaged in the purchasing, processing and distribution of Chinese herbal medicine. There are over 800 pharmaceutical factories employing over 80 000 workers. The area under cultivation of medicinal plants in 1983 was around 400 000 hectares, the amount of medicinal plants purchased annually at this time being around 13 million tons. It can be seen that for as gigantic an operation as this, the facilities needed for establishing an efficient quality control system will also be considerable. The Chinese authorities are well aware of the problems and constraints facing them in developing this system and are endeavouring to develop a system which would use the standards of quality required for the modern system of medicine and medicines without detriment to the practice of Chinese traditional medicine and use of herbal remedies in this system of medicine.

United Kingdom

All herbal medicines offered for sale for therapeutic purpose have to be approved by the Medicines Commission and registered by the appropriate authority. The requirements needed by the government are, in fact, quite different from those needed for synthetic drugs being introduced into the market for the first time.

Every medicinal plant or herbal remedy sought to be introduced for sale in the country – whether from within or from outside the country – is dealt with according to what is already known about the plant; whether there is some evidence that it acts as it is supposed to do, whether side-effects have been reported after use of the plant, or whether because of their structure, such side-effects could be expected and whether this plant substance is being used in other countries, and the experience in those countries is documented in scientific books or journals. Another aspect looked at is, of course, the conditions for which these are to be used. A plant substance which would be used for myocardial infarction would undergo much more rigid scrutiny than a plant substance to be used for backache or indigestion. Whether the introduction of this plant substance could affect the use of other life-saving medicines is also considered.

The Medicines Commission Secretariat, assisted particularly by the pharmacologist and the pharmacognosist, will review what is known about the plant and, in a spirit of pragmatism and tolerance – since plants have been used in the United Kingdom for centuries – decide whether the substance could be allowed to be sold in the country.

The authorities are aware that ethnic groups in the United Kingdom bring along their own herbal medicines – Ayurvedic, Unani or Chinese and are loth to interfere with their use so long as these medicines are restricted to use by the communities which have faith and belief in these remedies and this latitude is not misused by selling these products or advertising their use for therapeutic benefit. This attitude of tolerant and tacit agreement to the use of herbal medicines not registered in the United Kingdom, by ethnic migrant groups from India, Pakistan and Bangladesh has, by and large, been successful so far. Just as the United Kingdom was unique in regulating its use of allopathic medicines by a non-statutory "recommending" body, such as the Committee on Safety of Drugs, for many years, regulation of herbal remedies in the UK today is also being implemented in a semi-formal manner governed by attitudes of commonsense and understanding. However, just as the Committee on Safety of Drugs had to be replaced eventually by the more formal Medicines Commission, so also will clear-cut application of

well-formulated regulations have to be applied one day to the use of herbal remedies in the United Kingdom. That day is close.

The discussion above relates to plant substances already being used in other countries, perhaps for centuries. If a new plant substance, which has never been used before and about which nothing is known has been developed, then the requirements are the same as those required for a new synthetic chemical entity.

Plant substances which are available as food and drink, such as herbal teas, can be freely sold provided no claim is made in the literature accompanying the food or the teas about their therapeutic properties or indication for use. These do not have to be registered. It does not matter that in an adjacent area, even in the same shop there may be pamphlets or publications which extol the benefits and virtue of these herbal substances as therapeutic agents. If there is a therapeutic indication in the herbal medicines themselves, such as in the preparations marketed by the Seven Seas Company or the Herbal Products Company, then these have to be approved for registration. It would be fair to conclude that this system of "regulating" by "not regulating"; of "knowing" what is happening but not "interfering" unless absolutely necessary; of recognizing that ethnic groups need to use their own herbal remedies, can only work in the United Kingdom because of their own tradition in the use of herbal medicines, the country's historic background and experience as a colonial power in countries where herbal medicines have been used for centuries, because of the basic qualities of honesty, tolerance and commonsense and an attitude of "live and let live" in the people of the United Kingdom. Such a model should not be attempted elsewhere as it will probably not succeed.

Canada

Any substance administered for medical or therapeutic purposes in Canada is regarded as a medicine and all such medicines are basically subject to the same system of regulatory control. All these substances, including traditional herbal medicines, are reviewed by the drug regulatory authorities before approval is given for marketing them. The herbal substance could be a well-established drug from herbal sources like vincristine and vinblastine, it could be a plant juice like an extract of hawthorn berries or could be a herbal tea containing cammomile. All these medicines require a Drug Identification Number – just as allopathic synthetic drugs – and the same system is followed for applying for number and review of the application.

However, it is in the review process that there are differences in the requirements needed for the different types of medicinal plant substances. There

is a category known as "herbal medications" in which there is a sub-category of "traditional herbal medicines". Supporting data required by the Canadian drug regulation authorities in the application for introducing these substances in the market are less stringent than those required for conventional drugs. In accepting this principle, it is expected that these traditional herbal medicines will be used for minor self-limiting conditions. The Canadian stance has been clearly enunciated. "The Act does not distinguish drugs on the basis of origin, nor whether they are 'natural' or 'synthetic' but rather on the basis of the purpose for which the substance is manufactured, sold or represented". This is an excerpt from the Information Letter Number 771, dated 5 January 1990, from the Health Protection Branch of the Department of Health and Welfare.

The government, on receiving an application, has therefore to decide whether a substance is to be classified as a good, conventional synthetic drug, a conventional drug produced from herbal origin or a traditional herbal medicine. The requirements for their assessment will vary according to this. Generally, this depends on whether the substance has pharmacological activities. Those substances, devoid of pharmacological activity, could be classified as food.

Herbal remedies could fall, according to the Canadian regulations, into two groups. The first group consists of herbs and plants listed in the pharmacopoeias and which have pharmacological activity that has been well described. These substances are reviewed in the same manner as other conventional drugs. These could be drugs of herbal origin obtained in the market with only a prescription such as digitalis or a non-prescription herbal drug such as belladona. We are not so much concerned with this type of drug as we are with the review of traditional herbal medicines.

The national drug regulatory agency requirements, as has been stated earlier, are less stringent for these substances. Anecdotal or empirical evidence is accepted for this category provided that the supporting references have not been superseded by more recent research, study and publications. A remedy, such as the extract of hawthorn berries, if supported by anecdotal evidence of benefit and use, would be acceptable to the authorities unless something had been published regarding its lack of efficacy or possible toxicity. No evidence of efficacy nor of lack of toxicity – pharmacological and toxicological data – is required before approving such substances. However, if a claim is being made for a different indication than that mentioned in traditional literature, or if the drug is being used in a different manner from that described in the literature, then in these cases the applicant may be asked to provide evidence either of safety or lack of side-effects from the use of project used in the manner sought for that purpose.

The regulatory authorities will, of course, look carefully at the type of disease or symptoms which the traditional herbal remedy is supposed to cure. A plant extract about which very little is known in literature and sought to be introduced for the treatment of cardiovascular disease will be looked at quite differently from a plant extract being introduced for cough. Any herbal remedy which is advocated for the treatment of a serious disease would be expected to be supported by evidence from clinical trials demonstrating not only efficacy but also safety. For the plant extract advocated for use in cough, there should be some supporting background information from the literature indicating that it has been used for that purpose in the past or that it is being used for that purpose.

Again, a special review will be made by the authorities of traditional herbal remedies which are intended for use in pregnancy, lactation and children or "used under circumstances where the ingredients might interfere with critical medication or pose a hazard to persons with chronic physical disabilities".

It is interesting to look at the type of information required by the Canadian authorities for considering registration of these herbal remedies. In 1984, it would have been enough to identify the herb by its common name e.g. hawthorn berries, while the Latin name may also have been given, if desired, to identify the particular plant. In 1990, the requirements were that the herbal ingredients should be identified by both the common name and the botanical name. The medicinal ingredients and the non-medicinal ingredients are to be listed separately. The amount of substance being used should be stated; for example, if it is a tea, then the weight of herbs per teaspoon or per tea bag should be stated. The part of the plant used, e.g. leaf, should be specified as also the pharmacological properties described, if any, for that particular part of the plant. All references providing anecdotal, empirical or pharmacological support for use of the particular plant or part of a plant, including its earlier use, should be submitted. The recommended dosage has also to be submitted.

The proposed label for the intended traditional herbal medicine should also be included in the application. The labelling of medicinal products not generally familiar to the public should be clear and indicate precise instructions for use and the conditions for which the herbal remedy is recommended for use. This information should enable the consumer to judge whether he/she would like to use the particular traditional medicine.

The drug regulatory authorities have also prepared a document, "Guideline – Insurance of Drug Identification Numbers for Traditional Herbal Remedies", which very clearly brings out, in an easy, helpful manner, the points needed

in an application for a Drug Identification Number for products falling within the category of the traditional herbal medicine.

It is also the intention of the Health Protection Branch to develop and bring out a series of monographs for traditional herbal medicine to which the industry could refer. Such a monograph is not yet ready for review by the author but outlines of the proposed Short and Long Herbal Monograph Formats are given, with the permission of the authorities, in Tables 5 and 6 respectively.

Table 5. *Outline of the Short Herbal Monograph Format*

1.	Scientific name:
2.	Synonyms:
3.	Common names:
4.	Definition of drug: parts used:
5.	Chemical constituents (complete listing):
6.	Qualitative and quantitative control: • Certificate of authenticity (including scientific name, part of plant used, site of harvest, date of harvest and storage conditions) • Microscopic description of drug • Assays: procedure, what is measured, references
7.	Pharmacology (human studies relating to acceptable non-prescription drug claims)[1]
8.	Toxicology (human and animal studies, a precis of the long monograph)
9.	Acceptable claims/indications for non-prescription use, denoting those claims which are *supported by human data with an asterisk (*) and those claims supported by animal* data with a double asterisk (**); the other claims are based on traditional/folkloric use.
10.	Contraindications/cautions/warnings: groups at risk. Include a standard statement in most cases that the herb is not recommended for use in children under age 12, pregnant or lactating women.
11.	Dosage and directions for use: • Accept doses found in the British Herbal Pharmacopoeia in most cases • Pharmacopoeial and/or folk medicine doses • Doses specified for different dosage forms (e.g., extracts and tinctures), as well as "equivalent doses of crude dried herb" which is obtained by calculation when the specification of the extract or tincture is known. Specifications of extracts and tinctures (1:1, 1:10 etc) clearly stated. • Single dose, dosage frequency and total daily dose wherever possible.
12.	References:

[1]This component of the short monograph differs significantly from the long monograph.

Table 6. *Outline of the Long Herbal Monograph Format*	
1.	Scientific name:
2.	Synonyms:
3.	Common names:
4.	Definition of drug: parts used:
5.	Chemical constituents (complete listing):
6.	Qualitative and quantitative control: • Certificate of authenticity (including scientific name, part of plant used, site of harvest, date of harvest and storage conditions) • Microscopic description of drug • Assays: procedure, what is measured, references
7.	Pharmacology – review of available information (more complete than the short monograph)[1]
8.	Toxicology – review of available information (more complete than the short monograph)[1]
9.	Historical/traditional/folkloric claims for uses[1]
10.	Acceptable claims/indications for non-prescription use, denoting those claims which are supported by human data with an asterisk (*) and those claims supported by animal data with a double asterisk (**); the other claims are based on traditional/folkloric use.
11.	Contraindications/cautions/warnings: groups at risk. Include a standard statement in most cases that the herb is not recommended for use in children under age 12, pregnant or lactating women.
12.	Dosage and directions for use: • Accept doses found in the British Herbal Pharmacopoeia in most cases • Pharmacopoeial and/or folk medicine doses • Doses specified for different dosage forms (e.g. extracts and tinctures), as well as "equivalent doses of crude dried herb" which is obtained by calculation when the specification of the extract or tincture is known. Specifications of extracts and tinctures (1:1, 1:10 etc) clearly stated. • Single dose, dosage frequency and total daily dose wherever possible.
13.	Official pharmacopoeial preparations (USP, BP, NF and EP) – past and present.[1]
14.	Acceptable combinations – in general terms only, e.g. laxatives and carminativaes. Problematic combinations.[1]
15.	Closely related herbs, e.g. other varieties or other species.[1]
16.	References:[1] (Specific statements in the monograph should be numbered to relate to the appropriate reference, wherever possible. A general reference list could also be used.)

[1]These components of the long monograph differ significantly from the short monograph.

United States of America

In the United States of America, herbal remedies are referred to as homoeopathic remedies. All such remedies, because these are offered for treatment of a disease, are regarded as drugs. This means that if a herbal remedy is included in the United States Pharmacopoeia, the official Homoeopathic Pharmacopoeia or the National Formulary, it will be recognized officially as a drug. If it does not appear in any of these official compilations, it will still remain a drug but not an officially recognized drug.

The only way that a drug is approved for its intended use in the United States of America is by approval of a new drug application by the Food and Drug Administration. Up till now, no homoeopathic drugs have been approved for administration under a New Drug Application. This however does not necessarily mean that it is illegal to market these herbal preparations. These could be marketed without the approval of the Food and Drug Administration in certain circumstances. All marketed drugs have to be listed with the Food and Drug Administration.

The position in the United States of America is that there are many homoeopathic preparations in the market which have not gone through the process of approval by the Food and Drug Agency. Some of these may be mentioned in the pharmacopoeias concerned or in the national formularies. If so, these homoeopathic remedies are officially recognized but not officially approved for marketing. They are however marketed but not illegally. They are marketed as homoeopathic remedies recognized (if it is in the Formulary or Pharmacopoeia) but not approved for marketing. It is not illegal for use.

The United States Government did not, up till now, stringently regulate the use and marketing of homoeopathic remedies because, in the past, these have really been marketed only by a very few manufacturers on a very limited scale. These firms have been serving the need mainly of homoeopathic practitioners who needed these medicines. Further, these medicines have little or no labelling for the consumer. The labels were intended for use by the homoeopathic physician who would make a diagnosis and then either dispense the homoeopathic medicine himself or give the patient a homoeopathic prescription. The patient could have that prescription made out at a homoeopathic pharmacy.

It is difficult to know whether this system is largely used for what is commonly known as homoeopathic medicines i.e. small dilution of substance prescribed in the science known as homoeopathy founded by Hanneman, or whether it is also used for medicinal plant medicines and, if so, to what

extent. In other countries, herbal remedies are not known as homoeopathic drugs which, in fact, are not herbal. In the United States of America, the Act is labelled as Homoeopathy but covers herbal products. It may look confusing but is in fact quite clear.

There has, however, been a change in the use of homoeopathic medicines in the United States in recent years. The number of firms marketing homoeopathic drugs has increased. There has also been a great increase in the promotion of homoeopathic medicines. There has been an increase in the marketing of homoeopathic medicines as "over the counter" (OTC) drugs to be sold without prescription. Some of these homoeopathic drugs – whether strictly homoeopathic drugs or herbal remedies – are being marketed and promoted for use in serious conditions such as cancer and multiple sclerosis.

In these changed circumstances, it is expected that regulatory control on the use of herbal remedies in the United States will be changed and made more stringent in the near future. The change in the use of herbal/homoeopathic medicines was in fact documented by an inspection survey of homoeopathic practices in the USA, carried out by the Food and Drug Agency in 1981.

To summarize, in the United States, there is at this time minimal control over marketing of products from medicinal plants. A plant substance, whether listed in the pharmacopoeia or not, could be marketed in the country without approval from the Food and Drug Administration. The producer would need to list the substance, however, with FDA. This system has worked so far because it was used with care largely by practitioners of Hanneman school of homoeopaths. The situation has changed with large-scale production of actual medicinal plants as therapeutic agents, of more widespread use of Hanneman's homoeopathic medicines as "over the counter" medicines and by promotion. In these circumstances, it is inevitable that the regulations governing the use and marketing of herbal remedies, will, in the near future, become more stringent.

Australia

Regulations controlling the use of herbal remedies in Australia will be discussed in two parts. In the first section, the system which is being used in the state of Victoria (and has been used for the last 50 years) will be presented. Australia is moving to a central control for the regulation of import, manufacture and registration of drugs which would include herbal remedies. The new system will be operating for the whole country by the time this book is published. The regulations relating to these new regulations will be discussed

in the second part of this section. The reason why the present system in Victoria state is dealt with (even though it is being given up in Australia) is that it contains much to commend and the Victoria model will be considered with interest by countries trying to develop regulations of their own, both for synthetic drugs and for herbal remedies. Only control of use of herbal remedies will be discussed below.

In Victoria, all herbal remedies sought to be sold in the state have to be registered and the person selling that particular medicine has to apply for registration to the state drug authority. This application is then considered by an expert advisory committee which evaluates all applications using the criteria of quality, safety and efficacy.

The general rule appears to be that if a herbal preparation is not thought to be toxic and there is no clear evidence of efficacy, then registration is given to the plant substance provided that no claim is made citing the efficacy of any ingredient in the preparation. If any such claim for efficacy is to be allowed to be made to the public, then the committee has to be satisfied, from the clinical and scientific data provided, that the substance or ingredient has been shown to clearly demonstrate efficacy.

The toxicity of a herbal preparation governs the scheduling of it and hence its labelling and distribution as provided for under the Drugs, Poisons and Controlled Substances Act rather than being a prime consideration as a therapeutic substance or medicine in terms of its registration under the Health Act. Such registration still requires proof of efficacy before it can be given. This applies to the plant substance or any part of it intended for therapeutic use.

If there is one constituent in a combined herbal preparation which is known to be active whereas no such evidence has been shown for the others, then it must, for those other constituents, be clearly stated that those ingredients form part of a base containing those plant substances. It is clearly implied that these substances are just there - and that there is no evidence that these additional substances or plants either add anything or substract anything from the preparation.

The drug registration authority will usually not register any herbal preparation which does not contain at least one substance known to be effective and accepted as such by the Victoria Drug Regulatory Authority. A plant substance or a combination of plants - all of them not known to be toxic - and none of them having shown to be effective to the satisfaction of the authorities will not be registered and thereby not allowed to be sold in

the state of Victoria. This is where the Victoria Drug Regulatory system is perhaps superior to other existing systems and will not allow unnecessary harmless but ineffective herbal medicines to flood the market. This may prove attractive to other countries formulating, at the moment, regulations for the use of herbal remedies.

The guidelines issued by the Victoria Drug Regulatory Authority for Chinese and other Asian herbal ingredients may be of interest to such countries and is therefore reproduced below.

> "The identification of the constituents of many herbs used in eastern medicines has often proved difficult. Applicants will need to furnish chemical data to assist the Committee as information from local sources is elusive. Toxicity and efficacy data are expected where a claim is to be attributed to these ingredients. The Committee observes that many of the claims made for eastern medicines are exaggerated and are not acceptable. Foreign languages used on labels and pamphlets must be an accurate translation of the English language text".

If a herbal remedy is being sought to be used as a prescription medicine for a specific disease, the New Drug Application will be reviewed for efficacy and toxicity and quality in the same way as any synthetic drug.

In the United Kingdom, an anomaly exists as regards herbal teas and foods containing plant substances to be used for medicinal purposes. As long as the label does not specify the purpose for which these teas and foods are to be used, no registration is required. Teas and food being sold for the same purpose do not need to be registered if the labelling does not indicate the medicinal value of the package. This again is not completely logical as the teas, for example, would be taken by people for the same complaints and the toxicity of tea, if any, will be the same, whether the label indicates the therapeutic indication or not. The indication for use of a medicinal tea has little to do with the possible side-effects which could be induced by that particular tea.

The ease with which a herbal remedy is administered in humans in China and the rapidity of the transition from folklore use or use in a particular region to clinical evaluation is also not fully understood. A combination of plants, or single plant, which may be effective, may also induce serious side-effects and some toxicological studies need to be carried out before administering the medicine to the human for the first time under controlled conditions.

In the United States of America, there is a legal requirement that all drugs have to be approved for their intended uses through the approval of a New Drug Application (NDA) by FDA. Herbal medicines are drugs because these are used for the treatment of disease conditions. Yet, homoeopathic drugs, which include medicinal plant products, are legally allowed to be marketed, and, at this time, are also being promoted for use, without this being frowned upon. All that is required at this time is that all such medicines marketed for use are listed at the Food and Drug Administration "Y".

In Australia, when the new regulations come into effect, it will be possible only to "list" a new herbal remedy for conditions such as diarrhoea or for dissolving kidney stones without demonstrating any efficacy provided there has been no indication of toxicity. This may lead to a plethora of harmless but useless medicinal plant substances being approved for sale.

In spite of a few existing anomalies in the regulations of all countries, the broad general approach appears to be similar. Generally, countries are not much interested in regulating herbs and plant substances being prepared and used by individuals on a small scale. When such substances are packaged for use as teas or foods, the regulatory agency would like to be kept informed of what is happening and may or may not have a system of registration for these. When a herbal remedy has been in general use for a long time and is being used for a long time in the country, the regulatory authorities do not want to interfere or regulate the use of such a medicine. If a new substance is sought to be introduced for use in the modern system of allopathic medicine, the requirements in this instance will be the same as would be for a new synthetic substance.

It has sometimes been stated that the stringent requirements needed before clinical evaluation of traditional medicines are a constraint in the search for new medicines. While this may perhaps be true in a particular country, there is no evidence that generally the new drug regulations in countries act as such a constraint.

Past experience, in fact, has shown that national drug regulatory authorities are willing to discuss early clinical evaluation of possible new herbal remedies without fulfilling all the statutory requirements as regards prolonged toxicological studies on different species of animals and associated pharmacokinetic studies. It is, on the other hand, disappointing that despite this newer herbal remedies have not emerged in the last decade.

When the new federal regulations come into force, these will be applied throughout the country and the Victorian system of registration will be replaced

by the new system. The new law takes a less rigid approach by allowing herbal remedies to be listed on the basis of quality and safety. The national authorities will no longer look to see if there is at least one known effective substance in the medicine. Evidence for efficacy will not be required provided (a) the herbal medicine is not a poison on the schedule; (b) it is not in the attached schedule shown, and (c) no representation is made in relation to the disorders shown in the schedule put forward. Although the schedule is fairly exhaustive, it will be possible for herbal remedies to be marketed and therapeutic claims made for use of the remedies for conditions not in the schedule. All herbal remedies to be used in Australia are to be registered or listed in the Australia Register of Therapeutic Goods. In this system, herbal remedies could either be registered or listed with the federal drug regulatory agency.

General Review

It appears from the regulatory approach adopted by the six countries that demonstration of efficacy before registration and use of herbal remedies is generally not required. The lack of toxicity is considered more relevant. The only time demonstration of efficacy is required is when a herbal remedy – a new one – is introduced for use in the modern system of medicine. The approach to the assessement of safety of traditional herbal medicines sometimes varies in the different countries. It is not always easy to understand the logic behind the approaches used. A few apparent inconsistencies will be discussed.

The Indian authorities do not need any application for the registration of herbal medicines if these are prepared in exactly the same way as described in the ancient medical texts. The reasoning here is that if a particular medicinal plant preparation has been mentioned or described earlier in a treatise, then that preparation will not be toxic. It is difficult to accept this reasoning. It is possible that one or more of the medicinal plants used originally have now been shown to be toxic. To accept that a plant preparation is harmless just because it has been mentioned in an ancient text is not completely logical. Some assessment should be carried out before the herbal medicine is released and registered, and the release should, in fact, be dependent on the results of the assessment.

The Canadian authorities have less stringent requirements for traditional herbal medicines which would be used to treat minor self-limiting conditions. The reasoning is that a herbal remedy used for treating a minor self-limiting

condition is generally not harmful and therefore safe. The actual toxic effects associated with the use of a particular plant has, in fact, no relationship with the indication of use of that plant. A traditional herbal medicine to be used for treating mild allergy could induce more side-effects than a herbal medicine used for the treatment of cancer.

Many countries with no regulations at the present time are interested in developing such regulations controlling the use of herbal remedies and traditional medicines. These countries range from several countries in Africa and Asia where herbs have been used for generations for therapeutic purposes, to countries in the Gulf where there is increasing use of such substances. People in these countries are importing raw materials, preparing medicines and distributing these medicines, for example, in the Asian population in the Gulf countries. There is also a perception of the potential toxicity of chemical substances in the indigenous Arab population who may be interested in looking at some of the herbal alternatives available for use. Unless, however, some regulations for use of these crude substances and brand name plant medicines are introduced, the situation may well get complicated.

An attempt has been made by the Eastern Mediterranean Regional Office of the World Health Organization to develop a broad document to be used by countries when developing their own regulations. Representatives of nine countries in the Eastern Mediterranean Region of WHO assisted by the WHO Secretariat from Alexandria, drew up, discussed, formulated and adopted in their personal capacity broad guidelines for such regulations at an intercountry meeting held in Kuwait in April 1986.

This document "An Act aimed at ensuring the safety and quality of herbal remedies" (The Herbal Remedies Act) and Notes for Guidance can be obtained from the WHO Eastern Mediterranean Regional Office, Alexandria, Egypt (WHO/EM/Pharm/119-E). It contains an outline of an Act together with explanatory notes on different articles of the Act. In the second part of the document, there are notes for the guidance of persons applying for regulations of herbal remedies. These deal with general guidelines as well as specific guidelines required for the manufacture of finished products of single herbs or a mixture of herbs and herbs used as tablets, powders, liquids, tinctures and extracts. The document deals with quality control requirements: specification of raw materials, pharmacognostic and chromatographic characteristics. The document also describes the pharmacological and toxicological information required and, finally, quality control requirements of the finished product. Finally, there is in the Annex a Model Application Form which can be used for application and regulation of a herbal remedy. This is very useful to

national drug regulatory agencies interested in developing their own regulations for the use of herbal medicines.

The issues which have been discussed earlier in this section about the need for testing medicinal plants already in widespread use and the extent of toxicological and clinical evaluation before general use were also naturally discussed at length. This issue had already been discussed, before the Kuwait meeting, by the author and a few experts at a consultation held in Alexandria and the report printed as an EMRO document WHO-EM/Pharm/105 in 1985. The group prepared a set of "notes to the competent authority on toxicity requirements". These notes, which this author agrees with, are reproduced in the document containing the Act (document WHO-EM/Pharm/119-E), and which, together with the guidelines, are included in this publication with the permission of the Regional Director of the Eastern Mediterranean Regional Office of WHO as Annex.

Chapter 8
TWENTY-FIRST CENTURY

AS we move into the twenty-first century, the outlook does not look promising. The first International Congress on Medicinal Plant Research was held in September 1976 and its proceedings contain 283 pages of leads obtained from plants. Fourteen years later, not one of those leads have been extensively evaluated clinically. Fourteen years is a short time but it is difficult to see how things would improve unless thought is given to different approaches which could be adopted for drug development from herbal sources. At the first International Congress, it was stated that the challenge for such development "can only be met if, together with an improvement and refinement of methods of analysis, medicinal plant research is carried out on a broader interdisciplinary basis, with comparable, scientifically-recognized screening methods, and if it is better coordinated, with greater use of modern documentation means". There are no signs that these thoughts have been translated into action. One of the participants ends his presentation with the words "the chances of discovering new drugs from old plant remedies seem to be meagre, but so are the chances of discovering new drugs from synthetic compounds". Facts and figures often quoted by authorities that only 5 per cent of the 600 000 plant species existing on earth have been scientifically investigated or that in India alone there are 20 000 species, most of which should be looked at, appear meaningless when we do not even have a strategy for developing, rapidly, some of these plant substances into medicine.

There are certain issues related to medicines from plants which need to be highlighted. It has been said very often by persons interested in protecting the environment that if environmental pollution continues, our rain forests will be depleted and despoilt and a resource for developing new medicines from natural flora will be lost for ever. It is hoped that these same environmentalists would support research on some of the resources available. At the moment,

support is just not forthcoming for medicinal plants research even though such plant research would not require all the elaborate animal toxicology experiments now required for the development of synthetic compounds as medicines.

Only by looking at the past and by seeing the position today; only by knowing our weaknesses would we be able to plan for the next 50 years. At present, pharmaceutical houses are not really interested in getting back in a big way to medicinal plants research although they keep a fringe interest in it. These pharmaceutical houses possess the know-how of drug development even though this know-how is not always in the right direction in respect of medicinal plants research. We do not have the best researchers working in this field of work. There are not many opportunities for scientists to advance their careers if they choose this line of work. The infrastructure is weak. Centres of clinical pharmacology hardly exist in the third world where there is a history of use of these plants, a culture of use of herbal remedies and where these are being extensively used today. Clinical pharmacologists also do not exist in these countries. The methods being used are outmoded and crude and, by and large, developments in different areas of science and technology have not been taken advantage of by workers in this field of work. Most researchers are still carrying out screening of plant extracts on experimental animals using screening methods described in the early 1950s. The results of much of such work are not very helpful and could easily be misleading.

There is no sign of any international consortium or a joint programme involving WHO, the United Nations and the World Bank, for example, the Tropical Diseases Programme in the field of medicinal plants research.

When one turns away from research being carried out on plants for drug development to use of medicinal plants for use at the primary health care level, the problems facing us are different. There is this continued refrain that medicinal plants being used for the alleviation of symptoms and of illnesses at the primary health care level should be evaluated for efficacy. This insistence on testing by Western-trained scientists, moulded in the allopathic mode of thinking, of herbal remedies being used could be dangerous. It is not also feasible to carry out clinical evaluation of the thousand and odd preparations being used.

The second danger comes from the call for integration of traditional medicine with the Western system of medicine. If this attitude becomes more

prevalent and an attitude develops as "Integrate or Else", it is quite likely that the traditional medical practitioner will "or else".

If we are to progress, all the factors mentioned above will have to be taken into account. Let us now look at some of the positive things which are happening and then see what more could be done. The first positive factor is that there is a growing demand for herbal medicines and for support of research leading to the development of medicines from herbal sources. This is a force which could enhance resources for this line of work and even force research administrators to adopt a more realistic approach towards this research. This growing demand is not in the countries where such plants are being used but also in countries such as the USA, the UK, France and Germany. It is expected that the force of the conservationists and the organizations critical of research on animals will add to this force.

The second positive factor is that there still are several new medicines to be discovered from the plants around us. Even if organizations and national research councils may not know the best way to support medicinal plants research, yet all would agree that there are medicines which could be discovered from the world of plants.

A third positive factor is the availability of newer technology in adjacent areas. Such a technology could be used to make research on medicinal plants more effective. Some of these techniques like gas chromatography and mass spectroscopy to identify compounds present in the extract made from a therapeutic plant or tissue culture should be used in this field. This is possible because technologies exist.

A fourth positive factor is that some countries like India have realized that good, controlled clinical evaluation, after a limited toxicity study, forms a more realistic approach to medicinal plants drug development with experimental studies on a large number of animals with a large numbers of extracts.

The entry of Japanese scientists into the field of medicinal plants research on Kampo or herbal medicine is also a positive factor for this type of research. If the right quality of Japanese scientists take up this area for further work, supported by financial resources and modern technology possessed by the country, then the pace of research on medicinal plants could be hastened.

With this background of these prevailing positive and negative factors as we enter the twenty-first century, it will be possible to make some suggestions which could help in early development of medicines from plant sources. One

important step in any new approach is to wipe away the attitudes developed over years in the training provided by the Western system of medicine. This attitude will only be a constraint in attempting to use medicinal plants of future discoveries. Chemists, for example, need to get far away from their neat thinking of one plant, one compound. While this may be an intellectually comforting approach, it is still only the approach developed by the Western science. It may be totally inappropriate for research on herbal medicines. Pharmacologists have believed, over the years, in the screening approach based on the testing of many plant extracts on different animal screening tests. They need to get away from this approach to try and carry out some clinical trials on extracts already in use.

The Western-trained mind likes to have a compound from a plant based on animal screening because, for example, it is relatively easy to study the metabolism of a single substance when it comes into contact with the human body. The breakdown products of a single synthetic compound and the fate of the metabolic products can be easily determined by techniques such as use of radioactive substances. The position in plants may be different. Not only need there not be one active substance but the activity may be confined to a mixture or concoction containing several substances. In fact, these may all have to be in extract form to exert their pharmacological effect. Attempts should be made to accept these situations and to develop a methodology to utilize our special understanding about plants and how they act.

Once these attitudes are changed, then pharmaceutical houses need to be coaxed back to carrying out research on medicinal plants. However, this will not be of the type carried out by them from the 1940s till the 1970s. This would be selective research on one or, at most, two carefully selected plants. The pharmaceutical involvement, however, will not be easy because there would not be a patentable plant substance at the end of the road which will enable them to recoup the funds they would have put into research of the plants. It will be naive to expect the pharmaceutical industry to put in five to ten million dollars on research on selected plants if there is no patent.

International agencies, such as the World Health Organization, do not show any evidence of interest in obtaining large-scale support for this field. In these circumstances, it may be possible for the agencies to pool in resources and then ask the pharmaceutical industry to carry out toxicological and clinical research on a few selected plants and pay the pharmaceutical house for carrying out such research. The issue of patents and profits would undoubtedly have to be discussed and agreed upon and the same principles

which followed the Tropical Disease Research Programme of the WHO could be applied here.

It would be ideal if an innovative and imaginative research programme aimed at the development of a few selected herbal drugs is set up between an interested and leading University department, a pharmaceutical house and WHO and, if necessary, other United Nations organizations such as the United Nations Development Programme. University scientists have scientific leadership and could carry out much-needed work on newer methodology and basic mechanisms. The pharmaceutical house has the know-how of drug development in multicentred clinical trial methodology. The World Health Organization and the United Nations are certainly interested in the use of such herbal remedies in the third world which will help accelerate the pace of development of improved primary health care. A successful example of collaboration between a pharmaceutical house and the World Health Organization is the Tropical Disease Research Programme of WHO. Collaboration between a university department and a pharmaceutical house has always existed on a relatively small scale. However, due to the imaginative approach of the Professor of Pharmacology at the University of Oxford, a collaborative programme between the pharmaceutical house of Squibb and the Department of Pharmacology, Oxford, is being implemented. This alliance, signed in 1987, provides a sum of £ 20 million for the Department of Pharmacology over a period of seven years. A new building for the Department of Pharmacology, built out of these funds, has been completed and the Department has moved in there. Again, collaboration between WHO and the universities has been going on for a long time. What is now needed is leadership to develop a collaborative programme between these three complementing partners for developing medicines from plants. There are funds available for such an endeavour but what appears to be lacking is for some organization to take the lead. The example of the University of Oxford obtaining £ 20 million for one department demonstrates what can be done if an approach is made in the right manner.

National governments need to think about developing an infrastructure for research on medicinal plants. Centres of clinical pharmacology should be established and a group of clinical pharmacologists trained, perhaps with special reference to evaluation of medicinal plants in clinical trial methodology. In the field of primary health care, it is hoped that the governments will help traditional medical practitioners but will allow them to function outside the framework of the national health services controlled by specialists in the allopathic system of medicine. Governments could help them by providing

training to them by their own teachers and specialists, by ensuring that they always have a regular supply of herbal medicines of good quality and by giving them recognition for the service they are providing to the people in the country. This will be much more rewarding than insisting that all medicines used by them should undergo clinical evaluation for efficacy, that the two systems – allopathic and traditional systems of medicine – should be integrated and that the traditional medical practitioners be brought within the existing framework of national health services.

The steps suggested are not easy to take. Even if some of the steps like development of infrastructure or training of clinical pharmacologists are taken today, it will take time for such changes to make any impact. What is fairly certain, however, is that if these steps are not taken, the plants we have around us will not be fully utilized for the benefit of mankind.

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Annex

NOTES TO THE COMPETENT AUTHORITY ON TOXICITY REQUIREMENTS

HERBAL remedies may be broadly divided into three groups: (1) those which are well-known in the country and have been widely used for many years: (2) those which are not well-known but for which international experience is available; and (3) those which represent a new compound hitherto not evaluated as to its safety and efficacy. Obviously, different requirements for toxicological testing must be developed for these three groups.

For the first group, which consists mainly of products available in foodstuff or products which have been in use for a long time as traditional herbal remedies, requirements should be limited, if necessary at all. In general, it may seem unnecessary to require of the applicant proof of safety of the product. For the second group, views concerning the type of documents required to be presented may vary between countries. It is anticipated, therefore, that a variety of requirements will be elaborated for these products covering anything from reference in scientific journals confirming that the product is safe, to demands for limited or shortened toxicological tests.

The third group, covering the few cases where the authority is faced with a product not previously evaluated as to its toxicological properties, presents a delicate problem for the authority. There are two options: the authority may wait for convincing results of the product; or it may require that toxicological testing be performed by the applicant. In the latter case, the following guidelines[1] may be given to the applicants.

GUIDELINES

1. Introduction

State the name, complete composition, similarity to other drugs, pharmacological category, dosage form, route of administration, dosage, indications, contraindications, adverse reactions, interactions and precautions for preparation.

[1] Extracted from Draft Guidelines on requirements for registration of drugs, unpublished document (WHO-EM/Pharm/105), WHO EMRO, Alexandria (1985).

2. Single-dose Toxicity

Acute toxicity tests should be summarized (tabulated) for each species and route of administration. Toxic symptoms should be described as well as any other relevant information, e.g. cause of death. Any species or sex differences should be stated.

3. Repeated-dose Toxicity

Data should be summarized for each species, specifying the duration of the test and the route of administration. For each investigation, the dosage is to be stated as well as the number of animals per dose level, the sex of the animals and how frequently the drugs were given. The parameters studied, including laboratory tests and pathological investigations, should be stated, and all results relevant to the assessment should be summarized.

4. Pharmacodynamics

Studies of the primary pharmacological effects and modes of action forming the basis for the drug's recommended use should be summarized, with particular reference to quantitative aspects. The relations between dose and effects should be described. General pharmacological effects on vital body systems should be reported. Possible interactions with other drugs should be discussed.

5. Reproduction Studies

Investigations into teratogenic and other embryotoxic effects, peri- and post-natal toxicity, and effects on fertility should be summarized for each species and route of administration. For each study, the dosage, number of animals per dose level and period of administration in relation to gestation should be specified. The parameters studied during pregnancy as well as the methods used to examine foetuses should also be described. Maternal reaction should be reported as well as the drug's effect on the course of pregnancy and on the foetus.

6. Mutagenic Potential

The mutagenic potential must be considered in view of the chemical structure of the compound, mode of action, relationship to known mutagens and based on mutagenicity testing.

7. Carcinogenic Potential

The carcinogenic potential of the drug must be discussed. This should be based on the knowledge of chemical structure, relationship to known carcinogens, mode of action, mutagenicity studies and carcinogenicity studies

in animals. If epidemiological data or data from clinical trials are available, these must be carefully discussed. Data from animal studies must be summarized, stating animal species, dosages, route of administration, length of test, number of animals and the results statistically analysed.

8. Other Information

This section is intended for summaries of studies not covered by any of the previous headings e.g. tissue-irritant effects, sensitization, risks of addiction or dependency, specific toxic effects of comparison or different dosage forms.

9. Discussions and Conclusions

The manufacturer should state what conclusions can be drawn from the results. Pharmacological and toxicological observations should be discussed in the light of relevant scientific literature, paying particular attention to the drug's characteristics in comparison with those of any related previously known drugs. The pharmacological and toxicological data presented in this section should be evaluated in relation to the proposed clinical use of the compound. Both efficacy and risk aspects, as inferred from the pre-clinical documentation, should be considered.

10. Reference List

A list of cited pharmacological and toxicological documents should be enclosed. Any of these should be made available immediately on request.