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CONSULTATION ON POTENTIALS FOR USE OF PLANTS
INDICATED BY TRADITIONAL MEDICINE IN CANCER THERAPY

Geneva, 13-17 November 1978

[REPORT]

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1. INTRODUCTION

The meeting was opened with a statement by Dr CH'EN Wen-chieh, Assistant Director-General of WHO. Dr CH'EN extended cordial greetings on behalf of WHO and presented a brief historical background on events that led to the need for a consultation group on "Potentials for Use of Plants Indicated by Traditional Medicine in Cancer Therapy". Dr C. Olweny was selected as Chairman, Dr S. Natori as Vice-Chairman and Dr N. Farnsworth as Rapporteur to this meeting.

2. BACKGROUND TO THE CONSULTATION MEETING

A review of the collaborative UNICEF/WHO study concerning the health needs of the world, which was carried out in 1973/74 (report available from WHO), led to the conclusion that alternative methods must be mobilized and used to meet minimum health care needs in the developing countries, as opposed to the application of "Western" methods (including drugs), which are prevalent in the developed countries, and in most cases too expensive for use in the developing countries. Thus, the general emphasis at WHO is to develop programmes in health care that will make reasonable health care available for all of the people of the world by the year 2000. It has been conceded that the application of at least some of the elements of traditional medicine will be required to attain this goal.

In the field of cancer WHO is now obliged to pay more attention to the developing countries, where rising industrialization and decrease of communicable diseases is leading to a greater demand on cancer services with an increasing cancer incidence. This is why WHO's programme in cancer is more oriented to assist developing countries according to their expressed needs in the area of cancer services. The application of promising elements of traditional medicine for such a programme requires a new type of research approach. This consultation was therefore called in order to discuss, for the first time in WHO, the possibilities of such a research programme which could be executed mainly in the developing countries.

Plant and Plant Extracts

Many organic and inorganic chemical substances have been screened for anticancer activity by a variety of methods in several countries. The U.S. National Cancer Institute, alone, has screened well over 73,000 plants, in addition to other substances, in the past 18 years. Thus far, only the podophyllotoxins, Vinca alkaloids and colchicine have been applied in cancer clinical practice. The number of plants screened still represents only a small fraction of the possible millions of chemicals tested for antitumour activity in different countries.

The low yield is undoubtedly due to a number of reasons: 1) The basic biology of cancer growth is not fully understood. 2) Cancer is not considered to be a single disease entity but may be more than one hundred different diseases. 3) The search for active compounds has, to a large extent, been random. Taking into consideration the probable limits of surgery and radiotherapy, chemotherapy has much more to offer in spite of the relatively low numbers of valuable chemotherapeutic agents now available.

Plants and plant products have long been used in the treatment of various diseases. Medicinal plants have been an important source of useful drugs such as digitalis, cocaine, morphine and reserpine. In oncology, podophyllotoxins, the Vinca alkaloids, colchicines and some antibiotics are also derived from plants. The development of Western medical care has been associated with a decline in the direct use of plants as a source of drugs and medicaments. Once the chemical structures of the various plant substances are identified, scientists have turned their attention to the development of analogues and synthetic products.

Fortunately, however, there seems to be now a re-awakening of interest in the potentials of plant products for use in cancer therapy.

The variety of flora in tropical and subtropical regions is abundant and a substantial proportion is known to exhibit physiological effects, hence their applications as arrow and fish poisons. There is evidence to support the belief that folklore can be a useful tool in predicting plant sources exhibiting antitumour activity. Such indications have been observed for plants known to be poisonous and those known to have antihelminthic activity. Selection of plants for screening for antitumour activity, made on indications from folklore, increases the yield by a factor of two; antihelminthics by a factor of approximately three; and that of fish and arrow poisons by a factor of four and five, respectively. (Cancer Treatment Reports Vol.60, August 1976)¹. It is pertinent, therefore, that collections guided by folklore should be preferred to random collection.

In general, plant products evaluated for antitumour effects are usually extracted into any one of three solvents, namely water, alcohol and ether. If any of the solvent extracts shows biological activity against a tumour system it then becomes of considerable interest and merits further screening procedures. It is recommended that the new plant compound showing activity against any local experimental tumour system should, at the same time, be tested for activity on reference tumours, such as murine L1210 leukaemia and others, and that positive standard drugs for the reference screen, for example, cyclophosphamide and others, be employed in parallel testing with the candidate agent. (see WHO Document CAN 75/6).

Before a new active agent is ready for clinical evaluation, it must undergo toxicologic and pharmacologic evaluation. The actual detailed procedures, and the legislative requirements, vary from country to country. However, the general toxicologic information needed are the effects of the new agent on major organs like the kidney, liver, gastro-intestinal tract, and the bone marrow, and whether such toxicities are predictable, reversible and manageable.

Since different ethnic groups react differently to the same drugs, it is advisable that phase I clinical trials be carried out in different areas where the drug is to be used. Phase I studies are clinical pharmacology trials and are conducted with 30-50 patients and the initial dose is usually 1/3 of the toxic dose low (TDL) in animals, i.e. the first dose level measured in mg/m² of body surface that produces a degree of toxicity. They are designed to determine the maximum tolerable dose and possible damage to vital organs. Patients in the trial usually have advanced disease refractory to standard therapy. The disease does not need to be measurable although the investigator will be interested in any objective responses.

Traditional Medicine

The majority of the population in developing countries live in rural areas, while hospitals are located mainly in the towns and cities. Transportation difficulties, including cost, often coupled with misinformation and, in some instances, lack of knowledge of the usefulness of Western medicine, have contributed to many patients seeking medical care from traditional healers. Besides, their patients know very well that these healers have centuries of tradition, handed down to them from generation to generation, to support their practice. There is usually a cultural gap between the advocates of Western medicine who, in many developing countries, are often expatriates. Even if indigenous, their outlook and approach to certain health and allied problems may alienate them from their own community.

In some instances, cases of spontaneous tumour regression are ascribed to the healing powers of the traditional medicine man. The mechanisms are not well understood, but it is possible that the traditional healer, by some as yet unknown means, can stimulate the body's

¹ Spjut, R. W. and Perdue, R. E. Jr., Plant Folklore: A Tool For Predicting Sources of Antitumour Activity? (Cancer Treatment Report, 60, 979-985, 1976)

natural defences and bring about such regression.

Apart from these considerations, it is well-known that two, or more, disease states can present with similar symptoms; for example, an inflammatory process and a neoplasm may both present as a swelling. It is sometimes difficult to determine whether the tumour in question is either benign or malignant. The presence of concomitant inflammation may complicate the situation further. In order to substantiate the claims of cures made by traditional healers in such cases, accurate scientific diagnosis should be established, and an objective assessment made of the treatment results. The mere fact that such claims are made by healers should not in any way exempt them from scientific scrutiny.

It is essential that claims of positive results obtained by traditional healers be scientifically proven. The usefulness of the medication requires evaluation and, if found beneficial, should be further followed and developed. However, should they prove harmful to patients their continued use should be discouraged.

Collaboration

In the case of definitive activity by a plant extract or derivative, or a possible useful traditional healer's method, against a given cancer, a comparative study should be carried out using a standard regimen for that tumour. To achieve this goal, a dialogue must be established between the healer and the scientist and should be regarded as the first level of collaboration. The scientist should very tactfully convey to his "collaborator, the traditional healer", the absolute necessity for accurate diagnosis, plant identification; and the value of having results tested and repeated by others. Similarly, the scientist should endeavour to win the confidence of the traditional healer and make him appreciate that testing by others of his century-old tradition is not intended to deny him of his fame and livelihood, but will provide a means of sharing his wisdom and skills for the benefit of mankind. The scientist on the other hand should appreciate the fact that the local medicine-man is usually aware of which plants are active in any particular disease; what parts of the plants are used; and the best season for maximum yield of the active compound. In many instances exactly this knowledge is kept as secret.

A second level of collaboration can be organized, with the assistance of WHO, by setting up a network of Collaborating Centres in the various regions. An identified centre can perform the isolation, purification and preclinical tests. Since storage and transport to remote areas could lead to loss of some active principles, it would be advisable that the primary screening be performed in the country of origin of the plants. Reference may be made here to the ongoing collaboration between WHO and the Indian Medical Research Council in assessing the efficacy of traditional methods used in treating rheumatoid arthritis. The use of such existing facilities for a similar collaboration in a cancer programme is worthy of serious consideration and high priority.

Before a given compound is accepted for general usage its activity must be confirmed in several research centres. This standard procedure is a prerequisite for acceptance by the scientific community, and can be regarded as the third level of collaboration where WHO can again play a role as mediator and coordinator. Such testing in various laboratories by different researchers will also eliminate possible biases. This same principle should be applied to the actual methods used by the traditional healers, and any practice found to be in any way harmful should be discouraged and abandoned.

3. SUMMARY OF PAPERS PRESENTED BY INVITED PARTICIPANTS

3.1 The Value of Plants Indicated by Traditional Medicine in Cancer Therapy

Dr N. R. Farnsworth

The presentation stressed a need for multiple approaches to cancer treatment using plants arising from traditional medicine. A novel classification was proposed relative to the value that might be placed on information from "traditional medicine", i.e. traditional medicine

plants implied that they were used in an organized medical system, and involved diagnosis and prescribing by a qualified practitioner; ethnomedical plants derive from an indigenous system practised by a defined population, but diagnosis may not be involved; and folklore medicine plants would involve no medical system, but rather use by tradition within a poorly described population. Traditional medicine would be of greatest credibility and folklore medicine would be of least credibility, as indicated in this classification system. Brief mention was made of the adoption of a method by the Task Force on Indigenous Plants for Fertility-Regulation (Special Programme of Research, Development and Research Training in Human Reproduction/WHO) in which literature from these three systems, as well as in vitro and in vivo data on testing plant extracts for fertility-regulating activities were analyzed by computer to produce a rank-ordered priority list of plants for experimental work in each of the six Collaborating Centres set up by WHO for this purpose.

Whether or not plants have a real possibility of being useful for cancer treatment was substantiated by the fact that the Madagascan Periwinkle (Catharanthus roseus, syn. Vinca rosea) had provided two useful antitumour agents widely employed throughout the world, i.e. vincristine (leurocristine) and vincalkeboblantine (vinblastine). Recently, a physician-diagnosed case of Hodgkin's disease (biopsy) was observed to be treated with a crude plant extract of Catharanthus roseus in India. Further, a large number of plant-derived chemical compounds are entering into preclinical and toxicology studies in the NCI program in the USA, and some are in Phase I and Phase II clinical trials for cancer.

That direct information from the traditional healer would provide optimal information required for verifying efficacy of plant extracts as antitumour agents was pointed out in the following way. It is known that if plants are collected randomly and screened for antitumour activity in rodents, about ten per cent of all plants will show activity of sufficient interest to schedule them for further experimental studies. If plants are selected for the same animal antitumour tests on the basis of having been claimed useful as folkloric anticancer agents, about 20 per cent will show significant activity. Selection of plants on the basis of folkloric information that the plants have been used as anthelmintics results in 30 per cent having animal antitumour activity; based on having been used as fish poisons results in about 40 per cent being active; and alleged use as arrow poisons results in 50 per cent showing activity. Thus, a definite correlation of animal antitumour activity exists with certain types of folklore, all of which imply some type of toxicity or chemotherapeutic use. Thus, it can be anticipated that selection of plants used in traditional medicine by established practitioners, will reveal that at least 1/3 will have active principles that can be demonstrated experimentally in animal models.

Summary of Discussion:

A great deal of discussion revolved around the problem of defining terms involved with the use of plants as drugs by indigenous cultures. Many of these terms have been defined in WHO Technical Report Series 622.¹

Other aspects of the presentation were discussed, with the following general conclusions being drawn.

1. Effective involvement with traditional practitioners would necessitate development of appropriate lines of communication that were advantageous to both parties.

2. Since consideration of the value of each plant within the framework of specific cultures seems to present unmanageable difficulties, it was recommended that accepted pharmacological principles must be adhered to in the evaluation for efficacy.

¹ Technical Report Series 622: The Promotion and Development of Traditional Medicine.

3. A major problem envisioned was the interpretation of terms that would indicate that the disease being treated was indeed "cancer", since this is a relatively new addition to the medical vocabulary in traditional medicine, i.e. "swelling", "fomentation", "blood disease", etc. could all refer to a type of cancer, but not necessarily so.

4. Any recommendations should exclude the possibility of competing with existing major programmes to treat cancer, or to develop new anticancer drugs. For example, it would not be worthwhile to duplicate the random collection screening programme that has been ongoing in the USA for 15 years at the National Cancer Institute.

5. WHO should examine all of its programmes that involve the elements of traditional medicine, in order to avoid duplication and/or to consolidate similar aspects involving plant work and traditional medicine.

6. Cultural differences in response to cancer treatment should be afforded full recognition in any programme.

3.2 Natural Drugs Used in Spanish America for the Treatment of Cancer, Infectious and Parasitic Diseases

Dr F. Guerra

Dr Guerra discussed his many years of experience in the field of phytotherapy, including his views on traditional medicine as it is practised in Latin America. The discussions presented a variety of topics relating to the selection of plants through information available by practitioners of traditional medicine and/or users of the plants themselves. It was generally concluded that:

a) Of great importance is to initially prepare an inventory of plants alleged to be beneficial in the treatment of cancer.

b) Complete documentation on the exact Latin binomial of each plant should be acquired by competent botanists. Problems were anticipated because in many instances only fragments of plant material might be available, or the alleged useful preparation might be in an extract form. It was suggested that at least in some instances, chemotaxonomic data might give a lead to the identity of some plants, at least to the genus or family level. Clearly, however, identification and authentication of candidate plants was agreed to pose great problems.

c) It was also concluded that full documentation for all alleged uses for each of the anticancer plants should be acquired. There is evidence that conditions unrelated to cancer may have a positive correlation to actual anticancer activity, which would reinforce decisions to include plants in comprehensive programmes of study. For example, some data suggest that the alleged use of plants as arrow poisons, fish poisons, anthelmintics and/or insecticides, may have a close positive correlation with anticancer activity. However, without full documentation of these types of data, this added potential beneficial tool for the plant selection process would not be possible.

3.3 Research Strategies on Plants Used in Traditional Medicine for Cancer Therapy

Dr G. B. Marini-Bettolo

Major elements of a cooperative programme between the laboratory of Professor Marini-Bettolo and several South American countries were reviewed. Studies on anticancer plants in these cooperative programmes were reviewed also. Problems encountered, such as having insufficient of a plant sample to provide adequate identification, were again brought out, with the comment that chemotaxonomic information was at times useful in the establishment of plant identification, as well as to identify additional active antitumour plants. Recommendations

evolving from the discussions that followed are as follows:

- a) Prepare an inventory of all plants that could be useful for cancer treatment based on ethnographic reports.
- b) Acquire exact botanical identifications on as many of these plants as possible.
- c) Establish efficacy in some, presently considered as appropriate animal models.

3.4 Medicinal Plants used for Cancer Therapy and their Studies in Japan

Dr S. Natori

A number of complex multicomponent prescriptions evolving out of Chinese traditional medicine, but which were used in Japan, were presented in this report. In addition, a list of plants alleged to be useful in Japanese ethnomedicine has been presented. After discussions on several aspects of the presentation, the following general conclusions were made:

- a) Most of the plants indicated in Dr Natori's compilations contained chemical compounds usually associated with antitumour activity in animal models, i.e. lignans, quinoids, alkaloids, etc. However, testing of extracts in various animal models failed to reveal any that seemed worthwhile to study as candidates for clinical investigation.
- b) The problem of whether or not appropriate tumour systems, predictive for man, are useful for the determination of antitumour activity of plants in animals has been discussed. Although much discussion on this point followed, it was agreed that the question of appropriate tumour systems in animal models still remains an open area for search and at present time a clearly defined activity of the compound in several tumour systems is required for acceptance for clinical studies.
- c) One aspect of failure to demonstrate activity in a predictably active plant, i.e., one with good documentation as to human use, was envisioned as being due to lack of communication between the biologists involved in testing the plant extract, and the chemist preparing the extract. Clearly this lack of communication would have to be considered in any recommendation by the Group that might involve a need for testing for antitumour activity in animals.
- d) Plants containing high concentrations of "tannins" may or may not correlate with antitumour activity in humans. Tannins are generally thought to be toxic when injected, and erratic in their activity. In terms of external application, neither of these disadvantages would cause problems if an extract was used by humans. Clearly however, there is a need to study the structure/activity relationships of "tannins" and anticancer activity, because of the diverse chemical nature of this group of natural products. It was pointed out that some evidence is available showing that certain plant tannins are carcinogenic, but in all instances the route of administration has been parenteral when this effect has been demonstrated. Tannins have not been shown to be carcinogenic when administered to laboratory species orally.

Most clinically useful antitumour agents have also been shown to be carcinogenic. The reverse is equally true, based on animal experiments, but the reasons for these phenomena are unknown.

- e) Clarification was made on the topic of the relationship of pure cytotoxicity (in vitro) to in vivo activity against animal tumours, at least based on the 15 or more years of experience at NCI in the USA. Pure in vitro cytotoxicity, in the absence of in vivo animal antitumour activity, has no special significance relative to predicting human efficacy. However, it must be remembered that conventional chemotherapeutic treatment of human cancer is usually carried out with the antitumour drug being administered parenterally. Very often,

plants or plant extracts are mentioned as being used by traditional healers for the treatment of tumours by external application. In such instances, cytotoxicity may play a more important role, and thus this aspect of experimentally derived cytotoxicity data for plant extracts may have some useful correlation with efficacy.

3.5 Cancer and some Medicinal Plants Employed in Nigerian Traditional Therapy

Dr A. Tella

A summary of selected plants claimed to be useful in cancer treatment in Nigeria by traditional practitioners was presented. Some plants could not be identified relative to Latin binomial, and thus could not be included in the listing. Several of the plants are known to have antitumour and/or cytotoxic activity, based on literature reports. A number of the plants were not indigenous to West Africa and reasons for their introduction could not be clearly identified. Major points arising out of the presentation were as follows:

a) There is a need to acquire as many details as possible from traditional practitioners relative to the mode of preparation, specific dosing regimen, part(s) of plant used and additional details pertaining to the treatment modality. The method used to diagnose the condition being treated as cancer should also be documented.

b) The method of approach to the traditional healer is a decisive factor in soliciting truthful information. This is one of the most difficult problems regarding communication, cooperation and collaboration. The reasons for it are discussed later in the report.

3.6 The Structure-Antitumour Activity of some Bisbenzylisoquinoline Alkaloids

Dr O. N. Tolkachev

This paper dealt with the structure-activity correlation of selected bisbenzylisoquinoline alkaloids and some derivatives against a variety of animal tumours in vivo. Major structure changes including O-methylation and quaternization of the alkaloids of Michelia fuscata, e.g. magnoline and magnolamine.

Studies were initiated primarily on the basis of the previously known antitumour activity for this class of compounds, with efforts being directed toward enhancement of antitumour activity and/or decreasing toxicity. Major conclusions of the presentation were as follows:

a) Bisbenzylisoquinoline alkaloids are not oxidized by animals to electrophilic dehydro-derivatives.

b) Bisbenzylisoquinoline alkaloids were shown to possess antitumour activity of a different type from that one of the alkylating cytostatics.

3.7 New Approaches to Cancer Therapy

Dr A. Forbes

The summary of this paper dealt with a consideration of "unorthodox" modalities for treatment of cancer, with emphasis on the treatment of the patient, rather than the disease. Included were the elements of action of herbs due to the combined effect of several components; the protective effects of normally innocuous plant constituents against the effects of active constituents not normally considered innocuous; synergism of several components as existing in a plant extract. The possible adverse effects on active principles due to extraction methods; effect of climatic conditions, "astrologic" affinities and geographic factors on the activity of plants; "non-physical" energy fields of plants having a direct action on the same "energy field" of people they may be used to treat; and finally, adaptogenic effects of

plants, i.e. induction of non-specific resistance due to a plant mixture were all mentioned.

A great deal of discussion evolved, since this concept of natural "holistic" cancer therapy had not surfaced prior to this presentation. It was generally concluded that:

- a) There should be an open-mindedness toward consideration on new ideas, especially since many current modalities of cancer therapy are not effective. A scientific approach to all of the new ideas should be kept in mind in order to prove or disprove them.
- b) Avenues of effective communication should be devised between conventional research workers in cancer therapy and practitioners of "unorthodox" methods, herbalists, homeopaths, etc.
- c) Attempts should be made to include practising herbalists of known repute in subsequent advisory groups, to relay from personal experience their views on this mode of cancer treatment.

3.8 Antitumour Experiments and Clinical Observations of "757" - An Extract from Zhu-ling (Polyporus Umbellata)

Dr Chang-Jung-lieh

This presentation involved a discussion of the antitumour activity of an extract prepared from a Chinese basidiomycete, Polyporus umbellata, used in Chinese folk medicine, against the sarcoma 180 in mice. The purified extract was primarily composed of polysaccharide material. In vitro experiments showed that the extract did not appear to be acting directly on the tumour cells, and in vivo experiments indicated immunostimulation or immunopotentialiation as being responsible for at least some of the antitumour effects. The extract was effective by the i.m., i.v., or p.o. routes, either before or after tumour implantation. The extract was non-toxic in acute and sub-acute experiments, gave negative pyrogen and hemolysis tests, and failed to produce anaphylaxis in appropriate experiments in animals.

Significant symptom improvement and enhancement of immune function and/or survival times increases were recorded in over 300 patients with a variety of different types of cancer, during a two year study. During this evaluation period very few side effects were noted, especially a lack of bone marrow depression and leukopenia.

Fungi collected from seven different geographic areas in China were essentially equal in antitumour potency. However, insufficient mushrooms are available to meet the requirements for extended clinical studies. This prompted attempts to cultivate P. umbellata in laboratory culture, and to date it appears that this is feasible, since the hyphae elaborate antitumour substances.

3.9 On the Study of Antitumour Activity of Cephalotaxus hainensis Li and its Active Principles

Dr Han-Jui

Investigation of Cephalotaxus hainensis, a plant indigenous to China, for its antitumour activity and principles based on phylogenetic and folk medicine information has been performed. The following alkaloids were isolated: deoxyharringtonine, isoharringtonine, harringtonine, homoharringtonine, cephalotaxine, drupacine, demethylcephalotaxines, 3-epischammericine, epicephalotaxine, alkaloid IX and alkaloid X. Alkaloid IX and X were novel structures, but insufficient quantities precluded the structure elucidation of the latter base. In addition, a novel hexocyclic tropone lactone was isolated and given the name hainanenolide. It was shown to inhibit rodent tumours. The major alkaloid, harringtonine, was present in low yields (0.002% of bark), and was subject to a variety of biological evaluations, including toxicity studies, distribution, cytokinetic effects and mechanism

studies. On the basis of the animal pharmacological data, harringtonine was evaluated in human leukemia and lymphoma patients (more than 200), with promising results. A partial synthesis of harringtonine was carried out and the products studied pharmacologically. The semi-synthetic harringtonine has now entered Phase I clinical studies.

3.10 Ayurved, and the Administration of Semecarpus anacardium to Cancer Patients in India

Dr V. M. H. Barot

Ayurved is the main type of therapy used in India, and is involved in about 50% of the health care. About 30% of health care involves the application of orthodox medicine, about 5% homeopathy and 15% through other systems alien to and little understood by Western-trained medical personnel, e.g. Unani Tibbi, Hindu, Colour Therapy, Healing etc.

Each state in India has a director of Ayurved. The directorate is divided into three sections, Administration, Academic and Clinical Practice. Each Academic establishment has an enrolment of between 400-500 students, with a faculty-student ratio of approximately 3 to 1.

In Hindu philosophy, Brahman the absolute has three aspects: a creator (active) force, a negative (destroying) force and a preserving (unifying) force. In the individual human being, at a mental level, there are corresponding forces referred to as Gunas. At the physical level, there are three energies called Pitta (active), Kapha (negative) and Vayu (unifying); collectively these three activities constitute Doshas (Dosas). When all these elements are in balance, an individual is healthy. Disease occurs when the balance of these elements is disturbed by excess or deficiency. Imbalance can come about through unbalanced diet, physical activity, sleeping, sexual habits, climate, emotional states, physical surroundings, and/or age or sex of the individual.

Since Ayurved recognizes every person as a unique being, treatment is directed toward re-establishment of the balance. Hence, "true" medicines used to restore imbalances, according to the system do not give rise to side effects. First, there is a cleansing process, followed by administration of natural substances to restore the balance. Chants, Yoga, breathing and exercises are used in conjunction with herb administration as part of the balance restoration process.

The techniques of evaluation of the patient and his systems (balance) include a very detailed history, physical (including examination of urine, sweat, feces, sputum and voice) and pulse examination. In many respects, Ayurved is similar to the Yang and Yin theory of traditional Chinese medicine, but the former embraces more variables than the latter, and thus is more complex to use.

A preliminary study was described involving the use of "Bhallatak", the seeds of Semecarpus anacardium (Anacardiaceae), for the Ayurvedic treatment of 125 cancer patients. This plant had not previously been described as having been used in Ayurved for the treatment of cancer. However, it is described in this system as an agent to prevent old age and to alleviate "intractable" conditions. It has been known for some time that extracts of Semecarpus anacardium inhibit rodent tumours, based on periodical literature. This plant is currently being studied in the USA by the National Cancer Institute to isolate the active principles.

A jam prepared from S. anacardium seeds is currently being promoted in India for the treatment of cancer, but it is very expensive. The current study utilized whole crushed seeds in the form of a decoction, and is considerably less expensive than the jam.

All patients in the study were previously diagnosed at an orthodox medical hospital, many of them having been treated there previously and designated as terminal cases. Patients were assessed daily and weighed weekly.

For this study, a fresh decoction of the crushed seeds, prepared fresh daily according to Ayurvedic principles, was used. Clarified butter was applied to the mouth of each patient before and after each daily dose. Patients were maintained on a milk diet, supplemented with fresh fruits, such as grapes and papaya.

Based on signs and symptoms, the patients were assessed on a subjective rating basis of complete relief, good relief, moderate relief, slight relief and no relief. Subjective and/or objective tumour regressions were not included in the report, but pain and other symptoms appeared to be alleviated in about 50% of 97 evaluable cases.

3.11 Traditional Chinese Medicine and Cancer

Dr Han-Jui

Traditional Chinese medicine plays a major role in providing adequate health care for more than 800 million Chinese people. This traditional medicine system comprises about 85% use of herbal decoctions, including some animal, fungal and mineral drugs, and includes the use of acupuncture. The flora of China comprises about 5,000 species of medicinal plants, of which some 1,000 are in common use. Many of these medicinal plants have a history of use dating back some 30 centuries, however, some of the ancient records are unable to provide conclusive evidence that they were specifically indicated for the treatment of cancer. The reason for this is that recognition of cancer as a disease entity in terms of interpretable Chinese characters has been possible only in recent times. However, there are indications in traditional Chinese medicine for uses of plants or mixtures or plants as supportive therapy in cancer patients, i.e. to alleviate pain, promote appetite, produce a sense of well-being, activate the patient's natural resistance to infection, and others. Thus, traditional Chinese medicine has been principally used as a guide to identifying promising plants for inclusion in screening programmes against rodent tumours. In recent years, several hundred plants have been tested in this way, with promising results, for example, the recent work carried out in the People's Republic of China on the isolation and antitumour activity of harringtonine and other related alkaloids from Cephalotaxus hainanensis (Cephalotaxaceae).

Not all active antitumour agents isolated from plants through this approach have been shown to have practical applications. For example, the pyrrolizidine alkaloid monocrotaline was obtained from several Crotalaria species in China and was determined to have high antitumour activity against rodent neoplasms. Human use could not be considered, however, because of the hepatotoxicity of this alkaloid. Clearly, however, plants deriving from traditional Chinese medicine are proving useful as supportive therapy in cancer patients, as well as providing potential candidate compounds suitable for pre-clinical evaluation as antitumour agents.

Since a majority of the population in China reside in rural districts, and major medical facilities are not always available in sufficient numbers to serve the total medical needs, a system of health care using paramedical personnel has been used to advantage in treating uncomplicated medical problems. The now famous "barefoot" doctor is trained to treat those conditions which do not require major medical attention, as well as to recognize those conditions requiring referral to a higher level of medical care. Thus, in the case of cancer patients, the "barefoot" doctor refers them to a regional hospital or medical centre having the requisite facilities and personnel for optimal treatment. About one million "barefoot" doctors are utilized in the Chinese medical system.

3.12 Traditional Medicine and Cancer in Nigeria

Dr A. Tella

The traditional healer in Nigeria often specializes in specific medical problems, such as tumours including cancer, fractures, snake bites, dysentery, mental ailments and others.

Very frequently, cancer patients are treated with a mixture of herbs or herb extracts, concurrent with some form of ritualistic ceremony, incantations and the like. The ritualistic aspects of treatment often appear to be at least as important as the apparent therapeutic effect of the herb extracts.

Many traditional practitioners appear to possess a degree of sensitivity or extra-awareness, in some cases approaching extrasensory perception, not found in the general populace.

Traditional practitioners quite often acquire their skills through a long apprenticeship period, starting in early childhood. In many cases, the son learns from the father, who was instructed by his father, etc. Young children are closely observed for special traits before being selected as candidate apprentices. For example, special alertness, ability to concentrate, learning ability and memory appear to be natural attributes desired in the trainee. The apprenticeship may start by the child accompanying the father, a traditional healer, to the fields where he is allowed to observe the collection of specific herbs. At the appropriate time the son collects the herbs, under supervision, and ultimately on an independent basis. Observation of the use of the herbs and method of preparation for use eventually lead to a capability for independent utilization of the acquired knowledge and skills.

Knowledge of the use of appropriate plants acquired under described conditions usually constitutes the "secret" of traditional healers, and causes his reluctance to disclose it to others. Therefore the problem of communication between the traditional healer and even an indigenous physician is one of the more difficult tasks to be solved in order to obtain real, and valid information.

4. PROPOSED STEPS TO BE UNDERTAKEN FOR EVALUATION OF PLANTS USED IN TRADITIONAL MEDICINE FOR CANCER THERAPY

4.1 Inventory of Anticancer Plants used in Traditional Medicine

Following a discussion of the role of the Consultation Group in assessing the type and source of information that could be recommended relative to an appropriate inventory of anticancer natural products that might be suggested in the final report, four major types of information were considered essential:

1. Compilation of the Published World Literature (Non-Experimental) on Natural Products Relating to Anticancer Effects.
2. Compilation of the Published World Literature (Experimental Type) and In vitro Evaluation of Natural Product Extracts.
3. Guidelines for Collaborative Interaction with Traditional Practitioners on the use of Natural Products as Anticancer Remedies.
4. Compilation of Information on Traditional Methods for Cancer Treatment Involving the Use of Natural Products.

The Consultation Group recognizes that most of the WHO member states will prefer to organize and implement programmes to assess the value of natural products (including related treatment modalities), in an independent manner. However, it is highly improbable that any one country can assemble a majority of data, published or unpublished, that would be required to assist in making rational decisions on the most promising natural products to include in extended studies.

For this reason it is recommended that an exhaustive compilation of the world literature be assembled by WHO, in cooperation with member states, and that this compilation be made

available on request. It is further recommended that each country establish a National Advisory Group to evaluate any information on their indigenous anticancer natural products, for comparison with data acquired from the world pool of knowledge. WHO could offer expert advice in such matters on request from members states.

Thus, the Consultation Group gives strong support to the development of an exhaustive data base on all natural products that have potential relevance to cancer prevention, treatment, amelioration or cure, including traditional methods for prevention and/or treatment modalities. It is conceived that the available world information pool is extensive enough so that the most feasible and cost-effective method for organizing the data will be through computerization. Thus, the following data should be included in this information pool.

4.2 Published Literature (Non-Experimental)

It is well known that there are a variety of types of reports that suggest the value of natural products in the treatment of human cancer. Most of these concern the use of plants, but some data exists on animals, fungi and even minerals, as having value in the treatment of cancer. It is suggested that the world literature be acquired, starting with the extensive compilations of Hartwell (Lloydia 30: 379-463, 1967; 31: 71-170, 1968; 32: 79-107, 153-205, 247-296, 1969; 33: 98-104, 288-392, 1970; 34: 103-160, 204-255, 310-361, 386-438, 1971). These references provide more than 3,000 species with detailed information on their use. Other sources of information would also be explored.

Since WHO has an ongoing project to acquire information on all plants used in traditional medicine, and to eventually document all uses for these plants, it is recommended, that the responsibility for organizing and making available all of the data enumerated in this report be assigned to this programme, recognizing that adequate funds should be made available to augment the current study in order to accommodate the special needs of data on anticancer plants. The following types of information will be of greatest value for eventual analysis of the acquired data, bearing in mind that it will be rare when all of the elements listed will be available from any one reference.

1. Major taxon.
2. Latin binomial for each organism.
3. Author citation(s) for Latin binomial and/or synonym(s).
4. Vernacular names for the species relative to the country for which the vernacular name is appropriate.
5. Synonymous Latin binomials, where appropriate and known.
6. Country and area within the country where the plant used was grown.
7. Country and area within the country where the plant was used as a cancer remedy.
8. Part(s) of plant used.
9. State of plant when used, i.e. dried, fresh, extract of dried, extract of fresh, ashes, etc.
10. Method of preparing the plant or plant part for use in the treatment modality, i.e. decoction, tea, plant chewed and swallowed, etc.
11. Route of administration or application.
12. Frequency of administration or application.

13. Information on diagnosis of specific affliction, i.e. internal swelling, wart, ulcerous external lesion, etc.
14. Toxic or potential toxic effects.
15. Indications as to dietary restrictions, additions or modifications required as part of the treatment modality.
16. Age, sex, and race of the patient.
17. Other plants or materials used to augment the action.
18. Specific details relative to time or day, season of year, etc. when plant used is recommended for collection.
19. Data on prognosis as a result of the treatment.
20. Treatment is designed to:
 - a. alleviate symptoms
 - b. curative
 - c. other.
21. Contraindications to use of plants.
22. Treatment mode appears to be:
 - a. chemotherapeutic
 - b. ritualistic
 - c. dietary
 - d. other.
23. Treatment is involved in which (if any) organized indigenous medical system, e.g. Ayurvedic medicine, Chinese traditional medicine, etc.

4.3 Published Literature (Experimental)

There are three major categories of published (or potentially available to the WHO programme) data that would appear to be useful in the decision-making process relative to selecting natural products having the greatest probability for effectiveness in humans. Data indicative of positive, negative and/or equivocal test results are all judged to have potential value.

1. Results of in vivo Testing of Extracts of Natural Products for Antitumour Effects (including immunostimulant effects)

The world literature contains data (complete with specific testing conditions) on test results from hundreds of different species of plants, fungi, animals, marine organisms, etc. tested in laboratory animals. At least 700 species of plants are recorded, in readily accessible literature, as inhibiting various tumours in animals. For each positive or negative test result, it is important to record the following types of data (in addition to those items enumerated in 4.2 above):

- a) Tumour systems;
- b) Mode of tumour induction into test species;
- c) Time of tumour induction relative to initiation of dosing;
- d) Type of extract being administered;
- e) Route of administration;
- f) Dosage regimen;
- g) Quantitative results, i.e. per cent reduction in tumour size or volume, or increase in life span;

- h) Toxicity or limiting dose levels;
- i) Species used (including strain if given).

See WHO Document CAN/75.6 for useful information relative to the above.

Most investigators do not publish negative data. However, it is felt that repetitive negative testing for a given plant or other type of natural product, may be an indication that the preparation should be considered as a low priority lead, depending on a final analysis of all data.

The Consultation Group recommends that WHO establish working relationships with all member states known to be carrying out antitumour screening programmes involving natural products. Countries who either are currently involved in such programmes, or have been in the past (as judged from literature reports), as for example the National Cancer Institute (USA) which has negative test data on thousands of species of plants screened for antitumour activity over the past 15 or more years. Since these data are all computerized, little effort would be required to obtain copies of data for addition to the WHO documentation Programme on Traditional Medicine.

2. Results of in vitro Testing of Extracts of Natural Products.

Although it is not always possible to correlate in vitro (cytotoxicity) data with in vivo antitumour test results, it is felt that in many cases such information will be of value in the decision-making process relative to placing priorities on plants to be studied in detail for antitumour effects. Important information to catalogue would be as follows:

- a) Cell line employed;
- b) Type extract used;
- c) Quantitative test data, expressed as effective dose₅₀ (ED₅₀), inhibitory dose₅₀ (ID₅₀), or other relative indication of activity.

3. Results of Testing Extracts of Natural Products in Humans:

There are a few experimental studies reported in the periodical literature in which extracts of natural products have been evaluated in clinical trials involving human cancer patients. For example, Viscum album, Larrea divaricata, Eleutherococcus senticosus, etc. These should be acquired with data relative to the points enumerated in 4.2.

4. Chemical Compounds known to have in vivo and/or in vitro Antitumour or Cytotoxic Activity Reported to be Present in Natural Products used in Traditional Medicine for Treatment of Cancer.

A great deal of data are available on the in vitro and/or in vivo antitumour or cytotoxic effects of chemical compounds of known structure obtained from natural sources. Being able to associate these compounds with natural products in which they are known to exist, could be beneficial in providing a valid rationale for the use of the natural product in cancer treatment.

4.4 Guidelines for Collaborative Interaction with Traditional Practitioners on the Use of Natural Products as Anticancer Remedies

The Consultation Group recognizes the many problems attendant with establishing an effective line of communication with traditional medicine practitioners, especially as this relates to determining the identity of natural products and/or treatment modalities used by the practitioner in the management of cancer. It is apparent that mechanisms to establish effective relationships will vary from country to country, and will be influenced by government policy, socio-cultural, educational and allied factors. These guidelines would

appear to be most appropriately determined at a local level, with advice from a National Advisory Group set up within each country for this purpose.

The Consultation Group was made aware of a forthcoming WHO Report that appears to address this very issue. It is thus recommended that the National Advisory Group set up within each country, having a need to acquire information from traditional practitioners, should obtain copies of this report and use those elements of the recommendations which seem appropriate for local situations.

The Consultation Group would like to emphasize, however, that data obtained directly from the traditional practitioner will most likely be of the greatest value in determining promising plants for further organized study as aids in the treatment of cancer.

These recommendations have been made to provide a basic nucleus of information intended to be used for the rational and more effective application of the principles of traditional medicine in the management of human cancer.

WHO should be prepared to assist member states in this matter by providing appropriate expert advisers, on request, to work with National Advisory Groups set up within a given country, for the express purpose of organizing, planning and implementing these types of programmes.

4.5 Non-chemotherapeutic Approaches involving the use of Natural Products for the Management of Human Neoplastic Disease

The Consultation Group considered a great many modalities by which natural products may be used by traditional practitioners for the management of human neoplastic disease. These mainly involved situations in which natural products have been utilized in a manner in which any positive effects would most likely be induced through well-established chemotherapeutic and/or immunoregulatory mechanisms. Indeed, one might consider these as classical or conservative approaches. In an embryonic stage of attempting to identify guidelines for the development of effective and productive cancer management programmes through the application of traditional medicine in the developing countries, the Consultation Group has felt that a conservative approach must initially be taken. In other words, it seems most logical to firmly establish working guidelines most likely to produce effective chemotherapeutic agents as a result of being cognizant of the long experience of the traditional practitioner, than to use multiple approaches.

However, the Consultation Group feels that eventually all modalities applicable to, or arising out of traditional medicine, should be explored. For example, a large number of potential modalities for cancer control surfaced during formal presentations: still others resulted from extended discussions on this topic.

Further, the Consultation Group generally agreed that it would be inappropriate for them to consider cancer management modalities that did not involve plants or other natural products in a chemotherapy regimen, since the meeting was convened to consider the potential value of plants used in traditional medicine for cancer therapy. Some modalities were identified in which plants, plant extracts or other natural products were indeed involved in a dosing regimen, i.e. homeopathy, naturopathy, dietary and vitamin approaches. However, none of these approaches was considered to involve the utilization of natural products as classical chemotherapeutic agents, and thus were not considered as appropriate for inclusion in this report.

On the other hand, the Consultation Group would like to emphasize that an open mind must be maintained relative to consideration of any and all cancer management modalities, insofar as a rational basis for their application can be forwarded. However, the Group considered that these non-chemotherapeutic avenues, even though they might be applicable to traditional medicine, were inappropriate for consideration at this time.

5.0 PROPOSALS FOR FURTHER ACTIONS

The Consultation Group is of the unanimous opinion that plants¹ used for the treatment of cancer by practitioners of traditional medicine, or for conditions alleged to be cancer, represent promising candidates for further research and development efforts. Indeed, strong evidence can be forwarded in support of this viewpoint. For example:

1. Currently, the plant alkaloid leurocristine (vincristine, VCR) is considered to be the drug-of-choice in treating acute leukaemias in children. It is also a component in virtually every combination chemotherapy regimen used today; most chemotherapeutic approaches to cancer management now employ this modality. This alkaloid is still extracted from the leaves of the Madagascan periwinkle, Catharanthus roseus (L.) G. Don (Vinca rosea L.). Vincaloblastine (vinblastine, VLB), also obtained from the Madagascan periwinkle, is widely employed for the management of methotrexate-resistant Hodgkin's disease, and for choriocarcinoma. These examples clearly serve to illustrate that plants do contain useful substances for the effective management of human neoplastic disease. Why then should we expect that properly prepared and administered extracts of some plants, be incapable of similar effects?

2. A large number of promising antitumour agents derived from plants are currently being evaluated in pre-clinical toxicology animal protocols (baccharin, bruceantin, homo-harringtonine, indicine-N-oxide and taxol), or are currently included in Phase I and/or Phase II clinical trials, e.g. acronycine, podophyllotoxin glycosides, maytansine and vindesine (USA), 9-hydroxyellipticine (France) and harringtonine (People's Republic of China).

3. Promising antitumour agents which have been isolated from plants known to have been used by practitioners of traditional or indigenous medicine for the treatment of cancer, are indicated as follows:

| Plant Name | Country where used | Active Principle |
|--|--------------------|--|
| <u>Brucea antidysenterica</u> J. F. Mill | Ethiopia | Bruceantin |
| <u>Catharanthus roseus</u> (L.) G. Don | India | Vincristine, vinblastine, vindesine |
| <u>Cephalotaxus fortunei</u> Hook F. | China | Harringtonine, homoharringtonine |
| <u>Daphne mezereum</u> L. | Several | Mezerein |
| <u>Heliotropium indicum</u> L. | India | Indicine-N-oxide |
| <u>Jatropha gossypifolia</u> L. | Costa Rica | Jatrophone |
| <u>Maytenus buchananii</u> (Loes) R. Wilcox | Africa | Maytansine and related compounds |
| <u>Podophyllum peltatum</u> L. | USA | Podophyllotoxin glycosides |

¹ Use of the term "plants" is recognized to denote other natural products (fungi, animals, minerals), although plants are the predominant natural product employed in traditional medicine.

The above represent only a few of several similar type examples that could be cited. Although all of the plants cited above have been recorded as being used in traditional medicine, or as folklore remedies for treatment of cancer, research leading to the isolation of the active antitumour principle(s) was initiated through such knowledge only in the case of *Podophyllum peltatum*, which has a long reputation of having been used by American Indians for removal of skin tumours. This information prompted a study of the plant for its antitumour principles at the National Cancer Institute in the USA about 20 years ago. All of the other active antitumour principles were discovered through inclusion of extracts prepared from them in random selection antitumour screening programmes.

If a more rational approach for the selection of the above plants had been used, e.g. one based on information directly acquired from traditional practitioners who were using the plants for the treatment of cancer, the antitumour activities and the active principles most likely would have been discovered and put to practical use at least a decade earlier. In addition, a considerable cost would have been eliminated through reduction of numbers of animal tests that would have been required, and the earlier availability of some of them may have alleviated an untold amount of human suffering in cancer patients.

4. It is well known that when plants are collected randomly and subjected to expensive blind-screening protocols designed to identify antitumour activity in animals, an expected 10 percent of all plants tested in this way will show significant inhibitory effects against rodent neoplasms.

However, if plants are selected based on having been used as folkloric cancer remedies (not necessarily used by traditional practitioners), and then evaluated for inhibitory activity against tumours implanted in rodents, about 20 percent of the plant species show significant activity. A recent study involving test data derived from the evaluation of 226 species of plants having folkloric reputations as anticancer remedies, support this correlation. Thus, selection of plants based on written folklore records of alleged use to treat cancer, results in a doubling of the effectiveness of the selection process.

These data reinforce the contention of the Consultation Group that a well-planned cooperative programme with practitioners of traditional medicine, designed to study plants currently used to treat cancer, can only meet with success.

On the other hand, the Consultation Group feels that implementation of programmes involving studies of plants used by traditional practitioners for the treatment of cancer, must be initiated along strong scientific lines, and within the current limits of our knowledge in this field.

It is important to recognize that any programme to screen crude plant extracts on animal tumour systems must be scientific in design and well organized. It would be a failure if only antitumour activity would be evaluated. All symptoms and signs of biological activity should be notified. As a standard procedure, particularly if antitumour activity is found and toxicity levels established, or unexpected biological activity observed, a histological study of major organs should be performed. An unexpected biological effect of the crude plant extract could lead to discovery of substances of pharmacological importance for other fields of medicine than cancer. This aspect of screening should be kept in mind in designing and organizing such a programme.

It has been established that more than 3,500 species of plants are alleged to have been used by man over the millenia for the treatment of various types of cancer. Many of these reports may have appeared as a result of the use of plants in traditional medicine. A major issue concerning the credibility of these types of claims involves the question as to whether or not the condition being treated was really cancer. For this reason, the Consultation Group unanimously agrees that any programme designed to study the role and effectiveness of plants used by traditional practitioners for the management of cancer, must include provisions for establishing the malignant nature of the tumour being treated.

The recommendations to be presented in this report are based on WHO encouragement of member states to develop programmes for the verification of claims by practitioners of traditional medicine that certain plants are effective in the treatment of human cancer, as well as to establish the lack of such an effect if this is the case.

It is anticipated that concurrent practical and fundamental research approaches will be required, depending on the needs, resources and interests of a particular member state. To develop such programmes with maximum efficiency, the Consultation Group feels that member states should first establish one or more Traditional Medicine and Cancer Advisory Groups, which can work independently, but be assured of support, advice and encouragement from WHO.

Such Advisory Groups in member states should initially develop procedures for effective interaction with traditional practitioners. Next, botanical verification of the material being used must be assured, and all details concerned with preparation of the material used and mode of administration in the treatment regimen must be standardized. The next step would be to provide adequate documentation of the malignant nature of the disease being treated, followed by assessment of the clinical effectiveness of the traditional preparation.

Concurrent with initiation of treatment in humans, verification of the in vivo anti-tumour activity against one or more appropriate rodent neoplasms should be carried out. When this is established, fractionation by means of bioassay to the point of isolation and identification of the active principle, would naturally follow.

When clinical efficacy has been established by the traditional practitioner, efforts must then be directed toward standardization and determination of the stability of the preparation being used in humans. Other pharmaceutical and pharmacokinetic aspects normally considered in drug development programmes should follow. An adequate supply of the plant material would also have to be assured, and identification and control procedures established.

If human efficacy for the traditional preparation, and animal antitumour activity of the active principle are both established, consideration of the use of the active principle itself for the treatment of human malignancies, would have to be assessed.

Thus, the independent development by a member state of plant antitumour agents, based on initial verification of efficacy by the traditional practitioner, and further development along the lines suggested above, can offer many advantages, including (a) verification of the value of traditional medicine using established scientific principles, (b) reduction in medical costs to member states through the effective use of standardized active preparations for the management of cancer, (c) development of purified active antitumour agents for local use, or for export to other countries, and (d) strengthening of biomedical research capability within member states that can be eventually expanded and directed toward the development of drugs used in traditional medicine against other diseases and/or conditions of importance to the populace of the member states.

With this supportive background as an introduction, the Consultation Group concludes the following:

1. A Task Force on Traditional Medicine and Cancer should be established in order to provide WHO with the expertise required in developing appropriate recommendations and guidelines for future programmes in the area of traditional medicine and cancer, which may be requested by member states.
2. Collaborative research programmes should be encouraged by WHO within and between those countries of the world having an interest in the utilization and development of plants in the treatment of cancer by traditional practitioners. Criteria and guidelines for such programmes should be developed and made available to member states on request.

3. Encouragement should be given by WHO to member states in which traditional practitioners are using plants for the management of human cancer, for the establishment of programmes for the rigorous determination of efficacy for these preparations, based on modern scientific evaluation criteria. Verification of the diagnosis as a malignancy must be established in each case as an initial step. WHO should be prepared to provide advice and assistance in these matters when requested.

4. The current WHO project designed to acquire, catalogue and make available information on all plants used in traditional medicine, should be expanded to include data of the following types:

- a) All published literature relating to the alleged use of plants for the treatment of cancer. Exchanges of unpublished information of this type with member states should also be carried out.
- b) All published literature concerned with the in vivo antitumour activity and in vitro cytotoxicity of plant extracts (including negative data), as well as effects of a similar nature reported for plant principles of known constitution.

5. Symposia should be encouraged and supported in which traditional practitioners and scientists involved in research programmes on plants used in cancer therapy, will have an opportunity to interact and exchange views and ideas.